Klinische Wochenschrift

Organ der Gesellschaft
Deutscher Naturforscher
und Ärzte

67. Jahrgang · 1989

Springer-Verlag Berlin Heidelberg New York
London Paris Tokyo Hong Kong

Klinische Wochenschrift

Begründet 1922. Herausgegeben von V. Salle, A. Gottstein, A. v. Domaris, P. Jungmann, C. v. Noorden, H. Schwiegk u.a. Ab 1926 Organ der Gesellschaft Deutscher Naturforscher und Ärzte. Berlin, Springer und München, J.F. Bergmann.

Bildet die Fortsetzung der „Berliner Klinischen Wochenschrift", die von 1864–1920, herausgegeben von L.C. Posner, L. Waldenburg, C.A. Ewald usw. in Berlin, A. Hirschwald, erschien, und der „Therapeutischen (Halb-)Monatshefe", die von 1887–1921, herausgegeben von W. Heubner, L. Langstein, E. Meyer in Berlin, Springer-Verlag, erschienen.

Springer-Verlag Berlin Heidelberg New York London Paris Hong Kong Tokyo

Printed in Germany. – © Springer-Verlag GmbH & Co KG Berlin Heidelberg 1989

Druck der Universitätsdruckerei H. Stürtz AG, Würzburg

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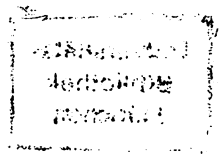

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Klin Wochenschr (1989) 67:452–455

Klinische Wochenschrift

Kasuistiken

Treatment of Secretory Diarrhea in AIDS with the Somatostatin Analogue SMS 201-995

H.S. Füeßl[1], W.G. Zoller[1], M.M. Kochen[2], J.R. Bogner[1], B. Heinrich[1], A. Matuschke[1], and F.D. Goebel[1]

[1] Medizinische Poliklinik der Universität, München
[2] Praxis für Allgemeinmedizin, München

Summary. We have observed two patients with AIDS suffering from severe watery diarrhea refractory to conventional medical treatment. In the first patient the reason for the diarrhea could not be revealed in spite of extensive investigations; however, the clinical picture suggested cryptosporidia infection. In the second patient cytomegalovirus could be shown in colonic biopsy specimens. After failure of several attempts of symptomatic, antibiotic, and antiviral therapy, the long-acting somatostatin analogue SMS 201-995 was administered to the patients subcutaneously in a dose between 2×50 µg and 3×100 µg/day. This treatment resulted in a prompt reduction of stool volume and bowel motions. Somatostatin may be a useful addition to the symptomatic treatment of refractory diarrhea in AIDS.

Key words: AIDS – Diarrhea, treatment – Somatostatin

Persistent diarrhea is a distressing problem in the clinical management of patients with AIDS. More than 50% of all patients with AIDS experience periods of prolonged diarrhea in the course of their disease [10]. In many reports no specific cause for the diarrhea was found in up to 42% of the patients reviewed, in spite of extensive diagnostic procedures [8]. Therefore, treatment of diarrhea has to be purely symptomatic.

Somatostatin has been useful in the treatment of secretory diarrhea related to various diseases such as Zollinger-Ellison syndrome [2], Verner-Morrison syndrome [3, 12], the carcinoid syndrome [5], glucagonomas [3], and ileostomy [18]. However, the native form of somatostatin has the disadvantage of a short half-life, necessitating intravenous administration [15]. Analogues of the peptide have been developed to overcome these problems [1]. A new long-acting octapeptide analogue of somatostatin, SMS 201-995 (Sandoz, Basel) is now available under a "compassionate need" protocol. The extreme stability against proteolytic degradation and a plasma half-life of more than 110 min ensure sufficient plasma concentrations of the peptide by only two or three subcutaneous injections daily. SMS 201-995 nonspecifically inhibits intestinal luminal secretion and prolongs mouth-to-cecum transit-time by more than four times [7]. We have studied the effect of SMS 201-995 in two patients suffering from profuse diarrhea in AIDS.

Case 1

A 40-year-old male homosexual (height 183 cm, weight 82.6 kg) being HIV-AB-positive (ELISA and Western blot) for 16 months reported increasing diarrhea, with initially loose stools gradually becoming watery over a period of 6 weeks. No blood or mucus was observed and no steatorrhea occurred. Frequent stool examinations for viral, bacterial, fungal, and protozoan pathogens were negative. His T4/T8 ratio at that time was 0.6. Treatment with high doses of loperamide, sulfasalazine, and spiramycin did not influence the diarrhea. Although the clinical picture was suggestive of cryptosporidiosis, cryptosporidia could never be observed in the stool or in colonic biopsy specimens. Within 2 months the patient's weight had come down to 65.3 kg. He was admitted because of dehydration and general malaise.

After admission we observed up to 80 bowel movements per day. The stool volume was between 4 and 5 l/24 h and fasting fecal output was more than 3 l/day. These findings indicate that the diar-

hea was due to a secretory process. On 40 mg opium tincture/day the motion frequency could be reduced to 10–15, however, stool volume remained unchanged. In addition, the patient complained of intensive pain during every bowel motion. A rectoscopy which had to be carried out under general anesthesia because of local anal pain showed two ulcerated anal fissures. The fissures had to be treated surgically. Rectal biopsy specimens gave a nonspecific proctitis without evidence for cryptosporidia; however, in a rectal smear clostridia were found. Accordingly, a treatment with metronidazole was begun, but without any effect upon the diarrhea.

Four months after onset of the diarrhea the patient's weight was 59.7 kg, meaning a weight loss of 22.9 kg despite fluid replacement and parenteral nutrition. Biopsy specimens of a total colonoscopy (again under general anesthesia), an esophagogastroduodenoscopy, and a suction biopsy of the small bowel were not diagnostic. A further trial with spiramycin did not influence the diarrhea. The patient complained of severe pain during each bowel movement, thus requiring opiates. In this desperate situation subcutaneous SMS 201-995, 50 μg twice daily was administered. The dose of somatostatin was chosen to correspond with previous work on the effects of the somatostatin analogue on the gastrointestinal tract in humans [5]. Within 24 h a prompt reduction of stool volume and frequency could be observed. Ten days after starting the SMS treatment the patient noticed one bowel movement per day. Twenty days after continuous SMS treatment a well-formed stool occurred. On discharge the patient's weight was 68.7 kg.

The total duration of the SMS treatment period was 3 weeks. Except for a light local pain at the injection site no side effects occurred. Routine laboratory parameters remained unchanged and in spite of the well-known depression of insulin secretion by somatostatin, an oral glucose tolerance test at the end of the SMS 201-995 treatment period was normal.

Amazingly, the diarrhea did not reccur after SMS 201-995 had been terminated. Even 2 years after the episode of diarrhea the patient is well and has reached his usual weight. His latest T4/T8 ratio is 0.4.

Case 2

A 29-year-old male HIV-infected homosexual with a history of *Pneumocystis carinii* pneumonia and Kaposi's sarcoma developed cytomegalovirus retinitis in March 1987 and was treated with ganciclovir for several weeks. A T4/T8 ratio of 0.09 and a complete lack of cutaneous reactivity indicated a severe immunodeficiency. In September 1987 the patient complained of 10–12 bowel movements per day with a total stool volume of 2000 ml. After failure of repeated specific treatment with ganciclovir and conventional treatment, including opium tincture, we put the patient on 50 μg subcutaneous SMS 201-995 twice daily. As no change in bowel motions occurred we increased the dose to 100 μg three times daily. Within 24 h the patient had only one bowel movement with a total stool volume of 730 ml. Stool volume could be maintained between 600 and 700 ml with one motion per day as long as SMS 201-995 was administered. SMS 201-995 was eventually withdrawn because the patient refused further subcutaneous injections which he experienced as rather painful. Only 4 days after withdrawal of the peptide we again observed seven bowel movements with a stool volume of 1500–2000 ml. Treatment could not be continued because the patient died from a general wasting syndrome. Autopsy revealed cytomegalovirus enteritis of the small and large bowel and Kaposi's sarcoma of the duodenum and rectum.

Discussion

Diarrhea can be the presenting syndrome or a life-threatening complication of AIDS. Although a recent study [16] could identify intestinal pathogens in 17 out of 20 patients with AIDS and diarrhea the contribution of these bacterial, viral, or protozoan pathogens to the pathogenesis of the diarrhea is not clear. In the remaining three patients no pathogen could be identified and in several other patients diarrhea did not subside in spite of specific therapy.

Even after careful evaluation we were unable to find the cause of diarrhea in the first patient. Though cryptosporidia could not be observed, we believe that the diarrhea was caused by a cryptosporidia infection because of several clinical features: The immense loss of water resulting in dehydration and weight loss, the absence of steatorrhea, the persistence of diarrhea in the fasting state, and the unremarkable findings at colonoscopy support this suggestion. The complete ineffectiveness of spiramycin is no argument against the diagnosis of cryptosporidiosis. In a recent trial more than 20% of all patients with AIDS and diarrhea due to cryptosporidia were unresponsive to spiramycin [13]. Other investigators maintain that there is no effective treatment for cryptosporidiosis [9]. If so, so-

matostatin could fill a therapeutic gap at least for treating the distressing symptoms in patients with AIDS and diarrhea.

The reason for the diarrhea in the second patient was most likely CMV enteritis. The pathogenesis organism could be isolated in the stool and the typical histological features were seen in colonic biopsy specimens and at autopsy. The stool volume was much lower than in the first patient, suggesting a lower secretory component than in the first case. Consequently, the effect of somatostatin upon stool volume and bowel motions was less pronounced even though a threefold higher dose was administered.

The reduction of stool volume in AIDS-related diarrhea is presumably effected by a direct action of somatostatin on the secretory cells of the gut. In patients with pancreatic cholera who have stool volumes comparable with our first patient's, a sharp reduction of luminal fluid flow in the upper jejunum and a shift from chloride secretion to absorption could be found on somatostatin [14, 6]. Thus, somatostation is particularly effective in situations of secretory diarrhea irrespective of the pathogen which may be an excess of vasoactive intestinal polypeptide or a cryptosporidial infection.

The improvement of the patient's diarrhea might also be related to a suppression of intestinal motility by somatostatin. It has been shown that the somatostatin analogue SMS 201-995 is able to prolong mouth-cecum transit-time fivefold in normal individuals [7]. This effect could be mediated by suppression of stimulatory gut hormones on somatostatin, such as motilin. However, a replacement of motilin by infusion did not overcome the effects of somatostatin on gut motility [11]. More likely, somatostatin has a direct local inhibitory effect on the myenteric plexus or the intestinal smooth muscle.

If the diarrhea in case 1 was related to an opportunistic infection, it is amazing that it did not recur after termination of the somatostatin treatment. A possible explanation is that as has been suggested [17], somatostatin may induce some cytoprotective mechanisms.

In a recent case report about a patient with cryptoporidiosis-related diarrhea in AIDS, a similar effect of somatostatin as in our patient was observed, however, treatment was continuously maintained thereafter [4]. It would be interesting to investigate whether the somatostatin analogue has any effect on the cultivation of cryptosporidia in the stool. Unfortunately, we can not answer this question in our case as we have only indirect evidence of cryptrosporidia being the causative agent for the diarrhea.

Irrespective of possible explanations and scientific arguments, we have found the somatostatin analogue SMS 201-995 to be highly effective in what is a desperate situation for patients. The successful management of diarrhea in these two cases warrants prospective clinical trials in order to further evaluate the indications for somatostatin analogues.

Acknowledgement: SMS 201-995 was kindly provided by Sandoz, Basel, Switzerland. The technical assistance of H. Heinlein RN is appreciated.

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Received: November 9, 1988
Returned for revision: January 3, 1989
Accepted: January 19, 1989

Priv.-Doz. Dr. H.S. Füeßl
Medizinische Poliklinik der Universität
Pettenkoferstrasse 8a
D-8000 München 2