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Subcutaneous octreotide versus oral loperamide in the treatment of diarrhea following chemotherapy

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Forty patients with chemotherapy-related diarrhea were randomized to receive (i) octreotide 0.5 mg three times per day s.c. or (ii) loperamide 4 mg three times per day p.o. until complete remission of diarrhea was achieved. In the octreotide group 80% of patients showed complete resolution of loose bowel movements within 4 days of therapy, while in the loperamide group this goal was obtained in only 30% of cases ($p < 0.001$). If after 4 days no benefit was seen, patients were considered to have failed antidiarrheal therapy. Failure was recorded in only one case (5%) treated with s.c. octreotide and in five patients (25%) who received loperamide. The mean duration of antidiarrheal therapy necessary to achieve remission was 3.4 days in the octreotide group and 6.1 days in the lorepamide group ($p < 0.001$). Treatment with octreotide was very well tolerated with mild abdominal pain in 15% of cases and pain in the injection site in 15% of patients. Subcutaneous octreotide is highly effective in the management of chemotherapy-related diarrhea in cancer patients.

Key words: Chemotherapy-related diarrhea, loperamide, octreotide.

Introduction

5-Fluorouracil (5-FU) is one of the cytotoxic drugs most frequently employed in the treatment of cancers of the breast, gastrointestinal tract and the head/neck region. Recently, several attempts have been made to improve the therapeutic effectiveness of 5-FU through the modulation of 5-FU metabolism employing drugs, such as folinic acid (FA),[1] interferon (IFN)-α [2] and hydroxyurea (HU).[3] The modulation of 5-FU has generally resulted in an improved response rate, but, unfortunately, also in an increase in gastrointestinal side-effects.[2,4–6] In fact, 5-FU-based chemotherapy may result in severe and sometimes life-threatening mucosal toxicity, especially in the form of stomatitis and diarrhea. Prolonged loose bowel movements may cause cancer patients to suffer from fluid loss, electrolyte imbalance, reduction in performance status and worsening of quality of life.[4] In many cases, patients with chemotherapy-related diarrhea require antidiarrheal therapy, prompt hydration and often hospitalization.

In the last decade octreotide, a long acting analog of the tetradecapeptide somatostatin, has been successfully employed in the management of diarrhea due to carcinoid tumors,[7,8] pancreatic and duodenal endocrine neoplasms,[9,10] and acquired immunodeficiency syndrome.[11] Recently, octreotide has also been reported to be active in chemotherapy- and/or radiotherapy-related diarrhea in cancer patients.[12–14] In this paper we report the results of a comparison between octreotide and oral loperamide in the management of chemotherapy-induced diarrhea in a series of patients with advanced carcinomas.

Patients and methods

All enrolled patients showed WHO[15] grade 3–4 diarrhea after chemotherapy. Patients had to fulfill the following criteria prior to being considered eligible for the study: oral informed consent, age ≤ 70 years, basal performance status according to Karnofsky Index ≥ 70, absence of fever $\geq 30^{\circ}C$, no contemporary use of analgesic therapy with opiates, no history of severe gastrointestinal disease other than neoplasm, no previous cardiovascular disease, no previous radiotherapy on the abdomen and no pre-treatment with other antidiarrheal therapy.

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Table 1. Patients' characteristics

	Loperamide	Octreotide
Number of patients	20	20
Age (mean) (years)	56	58
Sex (male/female)	11/9	13/7
Karnofsky Index (mean)	85	83
Number of patients with primary tumor		
breast carcinoma	4	5
gastric carcinoma	4	2
colorectal carcinoma	9	10
head/neck carcinoma	3	3

The main demographic and clinical characteristics of enrolled patients are depicted in Table 1. Nine patients with advanced breast carcinoma developed diarrhea during chemotherapy with FA 100 mg/m^2 plus 5-FU 400 mg/m^2 on days 1–3, plus epidoxorubicin 75–120 mg/m^2 and cyclophosphamide 500 mg/m^2 on day 1. Eleven patients with advanced colon carcinoma were given FA 100 mg/m^2 plus 5-FU 375 mg/m^2 plus IFN-α for five consecutive days. Six patients with advanced gastric adenocarcinoma received weekly FA 100 mg/m^2 plus 5-FU 500–600 mg/m^2 with oral HU. Nine patients with metastatic colon adenocarcinoma received 5-FU plus IFN-α. Six patients were given 5-FU 600 mg/m^2 on days 2–5 plus cisplatin 80 mg/m^2 on day 1 and vinorelbine 25 mg/m^2 on days 1 and 8 for recurrent or inoperable head and neck squamous cell carcinoma. Patients were randomly treated with (i) octreotide 0.5 mg three times per day s.c. or (ii) loperamide 4 mg three times per day p.o. Patients received loperamide or octreotide until complete remission was obtained. All patients were given oral hydration and dietary advice. However, if after 4 days of therapy no improvement was seen, patients were considered non-responsive (failure) and consequently hospitalized. In this case patients were given i.v. hydration with polyelectrolyte solutions. However, if progressive improvement was seen, therapy was continued until complete resolution was obtained. Duration of diarrhea was carefully recorded starting from the first day of administration of antidiarrheal drugs until complete disappearance of loose bowel movements was achieved. Patients were interviewed for subjective improvement and reduction in diarrheal symptoms, but partial response was not considered a response criteria because of potential bias due to the patients' self-assessment of the number of diarrheal episodes. Data were statistically analyzed by the chi-square test and Student's *t*-test.

Results

As depicted in Table 1, the two groups of patients were comparable in terms of demographic and clinical characteristics.

Sixteen (80%) out of 20 patients treated with s.c. octreotide obtained complete resolution of loose bowel movements within 4 days of therapy, while complete response was achieved only in six patients (30%) treated with loperamide. This difference was statistically significant ($p < 0.001$). In the octreotide group the remaining three patients had complete response after 4, 6 and 7 days of therapy, respectively, while one patient (5%) failed to respond after 4 days of therapy. The latter patient was subsequently given loperamide and responded after 4 more days. However, in the loperamide group the remaining nine patients showed complete resolution of diarrhea after 6 (one patient), 7 (two patients), 8 (two patients), 9 (one patient) and 10 (three patients) days, while five patients (25%) failed. These latter patients were treated with octreotide and all responded within 4 days.

In the group of responding patients treated with loperamide the mean duration of antidiarrheal therapy necessary to achieve complete remission was 6.1 days (range 2–6), while those treated with octreotide required a mean of 3.4 days of therapy until remission was achieved. Again, this difference was statistically very significant ($p < 0.001$).

Treatment with octreotide was quite well tolerated. Pain in the injection site was recorded in 15% of patients and mild abdominal pain in 15% of cases.

Discussion

Severe diarrhea is a relatively common side-effect of chemotherapy regimens, especially those containing 5-FU in modulation with other drugs such as IFNs and folinic acid.[2–4] Patients with chemotherapy-related diarrhea often require prompt hydration, antidiarrheal therapy and sometimes hospitalization.

Recently, some authors have reported that octreotide is very effective against chemotherapy- or radiotherapy-related diarrhea.[12–14] Kennedy *et al.*[12] showed that s.c. octreotide completely blocked diarrhea in 11 patients with advanced colorectal carcinoma. Petrelli *et al.*[14] reported complete resolution of diarrhea with continuous i.v. infusion of octreotide in 12 patients who had failed previous

treatment with diphenoxylate plus atropine. Although the mechanism of the antidiarrheal effect of octreotide is largely unclear, octreotide has been shown to reduce secretory diarrhea through the suppression of intestinal motility.[16] In fact a long acting somatostatin analog SMS-201-995 is able to induce a 5-fold increase in the mouth–cecum transit time.[16] This effect may be due to either a direct local inhibitory action on intestinal smooth muscle and myenteric nervous plexus or to the suppression of stimulatory intestinal hormones, such as motilin.[17,18]

In this study we compared oral loperamide to s.c. octreotide for the treatment of chemotherapy-related diarrhea. In the octreotide group, 83% of patients achieved complete resolution of diarrhea within 4 days of therapy, while at the same time only 31% of patients on loperamide had complete response ($p < 0.001$). The mean number of days of therapy needed to achieve complete response was significantly shorter in the octreotide group than in the loperamide group (2.8 versus 4.9, $p < 0.001$). These data are in agreement with those reported by Cascinu *et al.*[19] in a similar series of patients.

In conclusion, these data suggest that octreotide given s.c. is very effective in the control of chemotherapy-related diarrhea. Moreover, it may be safely given to patients undergoing chemotherapy also as out-patient therapy. However, we feel that it is advisable to start fluid replacement in any patient who complains of diarrhea for more than 4 days.

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