Bowel Rest, Intravenous Hydration, and Continuous High-Dose Infusion of Octreotide Acetate for the Treatment of Chemotherapy-Induced Diarrhea in Patients with Colorectal Carcinoma

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Background. **A prospective trial was conducted involving 16 patients with colorectal adenocarcinoma using a regimen of continuous-infusion octreotide acetate (Sandostatin [octreotide acetate], Sandoz, East Hanover, NJ) for the treatment of severe diarrhea induced by the weekly schedule of 5-fluorouracil (5-FU) in combination with leucovorin who were refractory to opiate therapy.**

Methods. **Fifteen patients had tissue-documented metastatic colorectal adenocarcinoma. An additional patient was treated adjuvantly. Fifteen patients were treated with chemotherapy consisting of 5-FU and high-dose leucovorin. The octreotide acetate regimen used was a continuous infusion of 50 μg/h for 12 hours followed by 100 μg/h for 12 hours and subsequently 150 μg/h for 72 hours. All patients were previous failures of diphenoxylate atropine (Lomotil diphenoxalate], Searle, Chicago, IL) given 2.5 mg orally after each loose bowel movement, but no more than 20 mg in a 24-hour period. Opiate therapy was not continued beyond 48 hours. All patients also were treated with bowel rest (nothing by mouth) and intravenous fluid hydration as well as octreotide acetate.**

Results. **Complete resolution of diarrhea was seen in 15 of 16 patients (94%). In 4 patients this was accomplished during the 100 μg/h infusion, and in 11 patients during the 150 μg/h infusion. Recurrence of diarrhea was seen in two patients after a complete cycle of octreotide acetate. Both patients were restarted at 150 μg/h for 72 hours of octreotide acetate with resolution of the diarrhea within 36 hours of the infusion. No toxicity related to octreotide acetate was seen in this trial.**

Conclusion. **The continuous-infusion regimen of octreotide acetate 150 μg/h is an effective and safe schedule for the treatment of chemotherapy-induced diarrhea together with bowel rest and intravenous fluid hydration in a group of patients in whom the majority were treated with the weekly schedule of 5-FU and high-dose leucovorin. *Cancer* 1993; 72:1543–6.**

Key words: octreotide acetate, diarrhea, intravenous hydration, infusion.

The modulation of 5-fluorouracil (5-FU) with high-dose leucovorin for the treatment of metastatic colorectal carcinoma has been associated with severe diarrhea. If the diarrhea is not treated immediately and aggressively, it can be fatal.[1] About 25% of patients treated with the Roswell Park 5-FU and high-dose leucovorin weekly regimen develop severe diarrhea.[1,2] Although in the majority of these patients, the diarrhea resolves with diphenoxylate atropine (Lomotil [diphenoxalate], Searle, Chicago, IL) and intravenous hydration, some patients remain refractory to this treatment.

Although the etiology of the diarrhea which results from the administration of 5-FU with high-dose leucovorin is unknown, octreotide acetate (Sandostatin [octreotide acetate], Sandoz, East Hanover, NJ) has a number of actions on the basis of which a beneficial effect could be postulated. Octreotide acetate inhibits such gut hormones as serotonin, vasoactive intestinal polypeptide, gastrin, insulin, glucagon, growth hormone, secretin, motilin, and pancreatic polypeptide which may contribute to the diarrhea.[3–6] Other pharmacologic effects occur which suggest that octreotide acetate has potential use in controlling severe refractory diarrhea. These include the property of regulating intestinal

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water and electrolyte transport, primarily, inducing net water and electrolyte movement to absorption.[7]

In view of these considerations, we have conducted a prospective study which evaluated the efficacy and toxicity of octreotide acetate for the treatment of severe refractory diarrhea (grade 3–4) secondary to chemotherapy in patients with colorectal adenocarcinoma. This treatment also included bowel rest (nothing by mouth) and intravenous fluid hydration as well as the high-dose continuous infusion of octreotide acetate.

Materials and Methods

Sixteen patients underwent treatment with octreotide acetate for chemotherapy-induced refractory diarrhea. All patients had an Eastern Cooperative Oncology Group Performance Status of 0 (normal) or 1 (ambulatory but symptoms present). Every patient developed diarrhea greater than or equal to grade 3 according to the National Cancer Institute Common Toxicity Criteria.[8] Grade 3 diarrhea was defined as seven to nine loose bowel movements in a 24-hour period. Grade 4 diarrhea was 10 or greater loose stools in a 24-hour period or grossly bloody diarrhea. All 16 patients failed a 48-hour program of Lomotil with no improvement of the diarrhea. This treatment consisted of 2.5 mg of Lomotil orally after each loose bowel movement, to a maximum of 20 mg/d for a total of 2 days. All patients were hospitalized and treated with intravenous hydration, nothing by mouth, and octreotide acetate within 48 hours of failing the Lomotil program.

Fifteen patients had tissue-documented metastatic colorectal adenocarcinoma, and 1 patient was treated adjuvantly. Patients received one of four chemotherapeutic regimens: (1) a weekly regimen of 6RS-leucovorin 500 mg/m^2 given in a 2-hour infusion followed 1 hour later by an intravenous bolus of 5-FU 500 to 600 mg/m^2: three patients; (2) a weekly regimen of a 2-hour infusion of 6S-leucovorin 250 mg/m^2 followed 1 hour later by an intravenous bolus of 5-FU 600 to 750 mg/m^2: eight patients; (3) a weekly regimen of 6RS-leucovorin 2.0 to 2.5 g/m^2 in a 24-hour infusion with 5-FU 1500 to 1800 mg/m^2 given as an infusion over 3 hours during the infusion of leucovorin: four patients; and (4) a combination of uracil and ftorafur 1200 mg/m^2 orally in divided doses given weekly: one patient.

Octreotide acetate was given to each patient in escalating doses. The dose of octreotide acetate was increased regardless of whether the diarrhea decreased, increased, or stopped. The regimen consisted of a continuous intravenous infusion of saline with octreotide acetate 50 μg/h for 12 hours then 100 μg/h for 12 hours followed by a 150 μg/h for 72 hours. If diarrhea recurred, an additional 72 hours at 150 μg/h was given. Response was measured by a reduction in the number of bowel movements and in the case of patients with a colostomy the total volume of fluid excreted in a 24-hour period.

Results

Sixteen patients were entered into the study. There were eight women and eight men. The median age was 57 years (range, 41–75 years). The mean loose stools per day was 8 (range, 4–20). One patient gave a history of four loose bowel movements 24 hours before admission which increased to eight loose bowel movements over the next 24 hours. All of the remaining patients met the toxicity criteria for grade 3–4 diarrhea. The definition of severe diarrhea in patients with colostomies was defined as continuous or multiple, loose, watery stools. The sites of metastases in 15 patients were as follows: liver, eight patients; lung, five patients; pelvic recurrence, one patient; and inguinal lymph node metastases, one patient. Patients with hepatic metastases had less than 70% tumor involvement of the liver and serum alkaline phosphatase levels less than three times normal. All patients with lung metastases had less than six lesions with the largest metastasis measuring 4 cm in diameter.

Complete resolution of the diarrhea occurred in 15 of 16 patients (94%). This complete resolution was seen in eight patients within 24 hours of the 150 μg/h octreotide acetate infusion, two patients within 48 hours of the 150 μg/h infusion, one patient within 72 hours of the 150 μg/h infusion, and four patients within 12 hours of the 100 μg/h infusion. Therefore, 11 of the 15 patients had complete resolution of diarrhea during the 150 μg/h octreotide acetate infusion. The single patient with incomplete resolution of diarrhea completed the 150 μg/h infusion for 72 hours and the number of loose stools decreased from 15 to 3 in 24 hours. This patient was subsequently placed on Lomotil 2.5 mg orally four times a day and a regular diet without recurrence of the severe diarrhea. Although this patient's diarrhea did not completely resolve, the improvement in grade of diarrhea is emphasized. Crampy abdominal pain occurred in all 15 patients who had complete resolution of the diarrhea. The crampy abdominal pain did not disappear until the diarrhea had completely resolved. This was true in the four patients who resolved their diarrhea within 12 hours of the 100 μg/h infusion.

Of the 15 patients who had complete resolution of the diarrhea with the escalating doses of octreotide acetate, 2 patients had recurrence within 48 hours of starting a regular diet. Both of these patients were restarted with octreotide acetate 150 μg/h for 72 hours and were kept with nothing by mouth. The diarrhea completely resolved in both patients within 36 hours of the infusion. One of these patients had a colostomy secondary

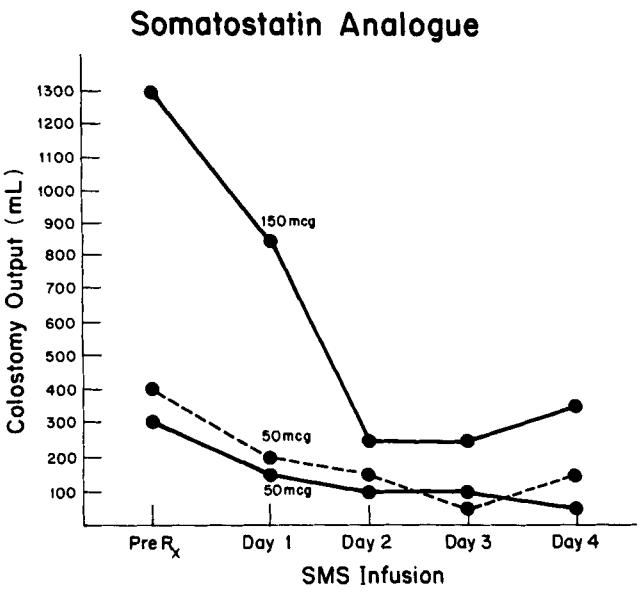

Figure 1. The patient, with colostomy output of 1300 ml, had recurrence of diarrhea after the octreotide acetate escalation from 50 μg/h × 12 h to 100 μg/h × 12 h to 150 μg/h × 72 h. This patient was restarted at 150 μg/h × 72 h with a dramatic decrease in colostomy output, as illustrated. The other two patients demonstrate a significant decrease in colostomy output during dose escalation of 50 μg/h × 12 h to 100 μg/h × 12 h to 150 μg/h × 72 h. SMS: Sandostatin.

to a previous abdominoperineal resection and within 36 hours of the infusion the colostomy output decreased from 1300 to 250 ml. Three of the 16 patients had colostomies and the successful response to octreotide acetate is illustrated in Figure 1.

No toxicity was seen with this continuous-infusion regimen of octreotide acetate. Concerning adverse effects, no transient nausea or pain occurred at the injection site during this continuous-infusion regimen, nor did other side effects occur. Despite successful treatment of the chemotherapy-induced severe diarrhea, patients were not maintained on the same chemotherapeutic dosages. All patients underwent dose reduction of their chemotherapy according to the criteria for grade 3–4 gastrointestinal toxicity. This consisted of a 2-week rest period followed by resumption of the 5-FU at a 20% dose reduction with no reduction in the leucovorin dose. The octreotide acetate continuous-infusion regimen was not used to maintain or increase the initial chemotherapeutic dosage.

Octreotide acetate is supplied in 100-μg ampules (1 ml) and 50-μg ampules (1 ml). The cost of each ampule is $6.12 and $3.34, respectively. Hence, the cost of one complete infusion regimen was $795.00.

Discussion

Octreotide acetate has been shown to control diarrhea in patients with the carcinoid syndrome and vasoactive intestinal polypeptide secreting neoplasms.[9–12] Reports in the literature suggest efficacy in control of diarrhea in patients with gastrinomas, glucagonomas, and insulinomas.[9,10,12] It has also been used to treat diarrhea in acquired immune deficiency syndrome and severe ileostomy diarrhea.[13–16] The mechanism by which octreotide acetate inhibits the diarrhea is unknown. Possible mechanisms include inhibition of gastrointestinal hormones, prolongation of intestinal transit time, and regulation of intestinal water and electrolyte transport.[6] Notice that a delay in intestinal transit time is the only mechanism by which opiates are recognized to possess an antidiarrheal effect.[7] In view of these actions, octreotide acetate has been found to be useful in treating diarrheal states of many diverse etiologies that are chronic and refractory to traditional therapeutic agents. Our group has reported preliminary results with the use of octreotide acetate for patients with metastatic colorectal adenocarcinoma who developed severe diarrhea from the modulation of 5-FU with high-dose leucovorin refractory to opiate therapy.[17,18] Our previous work[17,18] used the same escalating doses of octreotide acetate as described in this report. The rationale for using the continuous-intravenous infusion was to deliver the drug as rapidly as possible to treat the diarrhea. Our previous treatment of severe chemotherapy-induced diarrhea (Petrelli N, Herresa L, Creaven P, Rustum Y. Unpublished data, 1989) by bowel rest, Lomotil, and intravenous hydration alone has been successful in about 70% of patients. About 60% of patients who do not respond to this treatment will develop fatal toxicity. Because of the inability to determine the subgroup of patients who will not respond to bowel rest, Lomotil, and intravenous hydration alone, we decided to treat all patients who developed grade 3–4 diarrhea with the octreotide acetate.

In the current series, 15 of 16 patients had complete resolution of diarrhea during the escalating doses of octreotide acetate. Eleven of 15 patients had complete resolution of the diarrhea during the 150 μg/h infusion and 4 additional patients during the 100 μg/h infusion. These four additional patients continued with the escalation of the octreotide acetate through the 150 μg/h infusion for 72 hours. These results—inclusive of the two patients who had recurrence of their diarrhea after octreotide acetate escalation but when restarted at 150 μg/h had resolution of their diarrhea—attests to the fact that 150 μg/h is an effective and safe schedule. The 50 μg/h and 100 μg/h infusions were continued for only 12 hours because we believed that we were starting at a subtherapeutic dose and rapid escalation was necessary to control the severe diarrhea. Our next trial begins patients with refractory chemotherapy-induced severe diarrhea at 150 μg/h for 72 hours. We do not have any experience utilizing the current regimen of

octreotide acetate for other types of diarrhea such as radiation-associated diarrhea.

The recommended mode of administering octreotide acetate is via subcutaneous injection two to three times per day. Octreotide acetate has been administered via intravenous bolus injection or infusion in an emergency situation such as the carcinoid crisis.[11] The suggested daily dosage of octreotide acetate during the first 2 weeks of therapy of carcinoid tumors ranges from 100 to 600 μg/d in two to four divided doses. Clinical and biochemical benefits have been obtained in some patients with as little as 50 μg whereas others require doses as high as 1500 μg/d. However, experience with doses above 750 μg/d is limited. The continuous-infusion regimen of octreotide acetate that we have reported was chosen because of the urgency and potentially fatal results of patients who developed severe diarrhea from the modulation of 5-FU with high-dose leucovorin. Since immediate and aggressive treatment was needed, the intravenous route was chosen. Notice that octreotide acetate differs from native somatostatin in three significant ways: (1) octreotide acetate has a half-life of 60 to 112 minutes with a duration of action of 6 to 12 hours whereas somatostatin has a half-life of only 1 to 2 minutes; this explains why the subcutaneous injection of octreotide acetate has been effective for the treatment of chemotherapy-induced diarrhea[19]; (2) octreotide acetate inhibits growth hormone secretion preferentially to insulin secretion; and (3) octreotide acetate is less associated with rebound hypersecretion of hormones when its effect tapers off.[6] In view of the latter effect, we did not see any rebound diarrhea in any of our patients treated with the continuous infusion of octreotide acetate.

The subcutaneous injection of octreotide acetate 50 μg twice or three times a day has been reported to be successful in the treatment of severe diarrhea induced by 5-FU and high-dose leucovorin.[19] A randomized trial comparing subcutaneous administration of octreotide acetate with standard Lomotil in patients with colon carcinoma receiving 5-FU and leucovorin is ongoing by the Southwest Oncology Group (Leichman C, Fleming T, Muggia F, Aradalan B, Doroshow J, Tangen C, et al. Unpublished data, 1992). A prospective randomized trial is needed to compare the efficacy of the subcutaneous versus the continuous-infusion route, as described in our report. This prospective trial would also need a control regimen of patients treated with intravenous hydration, nothing by mouth, and opiate therapy.

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