Octreotide Long-acting Formulation (LAR) in Chronic Loperamide-refractory Diarrhea Not Related to Cancer Treatment

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Abstract. Objective: The effectiveness and improvement in quality of life (QOL) of a long-acting formulation of octreotide (LAR) administration for cancer patients, with chronic loperamide-refractory diarrhea not attributed to medical therapy, were investigated. Patients and Methods: Twenty-nine patients with chronic loperamide-refractory diarrhea were enrolled to receive octreotide LAR at a starting dose of 30 mg i.m. every 28 days until resolution of the diarrhea for a period of 3 months. Results: Twenty-three patients (79.3%) administered octreotide LAR achieved resolution of diarrhea, while six patients (20.7%) successfully controlled their diarrhea during the study. All patients experienced improved sodium, potassium, albumin and total protein values with improvement in their QOL, as assessed by the Linear Analog Scale Assessment (LASA) (mean values at baseline and at 3 months: energy: 3.2±1.1 vs. 6.2±1.4; function: 3.1±1.3 vs. 6.2±1.2; QOL: 3.2±0.9 vs. 6.1±1.4). No toxicities associated with the administration of octreotide LAR were noted. Conclusion: The administration of octreotide LAR at a starting dose of 30 mg i.m. every 28 days efficiently resolved or controlled chronic loperamide-refractory diarrhea, not caused by medical intervention, in cancer patients and improved their QOL.

Diarrhea in cancer patients is often under-recognized and therefore remains untreated, affecting the quality of life (QOL) and sometimes, if chronic and refractory, is life-threatening. Diarrhea in these patients is most commonly induced by treatment, including chemotherapy (e.g., 5-Fluorouracil, capetabine, oxaliplatin or irinotecan), surgery (e.g., Whipple procedure, gastrectomy or celiac plexus block), radiation therapy (enteritis caused by irradiation to the abdomen, para-aortics, lumbar and pelvis), or bone marrow transplantation (1). Other causes of diarrhea (acute or chronic) in cancer patients include the underlying cancer (carcinoid syndrome, colon cancer, lymphoma, medullary carcinoma of the thyroid and pancreatic cancer), antibiotics, dietary responses (e.g., caffeine-containing products or high-fiber foods), concomitant diseases (diabetes, hyperthyroidism, inflammatory bowel disease or tumor-related obstruction) or the stress and anxiety associated with cancer diagnosis and treatment (2).

The causes of diarrhea are also categorized by putative underlying mechanisms. These include exudative (e.g., excess blood or mucous enters the gastrointestinal tract), malabsorptive, dysmotile, osmotic and secretory (due to increased secretion of electrolytes and fluid) factors or a combination of them (3).

Because of the potentially life-threatening nature of diarrhea, rapid and thorough assessment is imperative. The goal of antidiarrheal therapy is to reduce fluid loss in the stools by inhibiting intestinal secretion, promoting absorption and decreasing intestinal motility. To date, the management of diarrhea includes hydration, electrolyte replacement and several antidiarrheal agents (intestinal transit inhibitors, intraluminal agents, pro-absorptive agents, and antisecretory drugs). Among these agents, loperamide is regarded as the standard treatment when given at a dose of 4 mg initially, followed by 2 mg every 2 h or after each unformatted stool, with a maximum of approximately 12 mg/day (4-7).

Octreotide, a somatostatin analog with antisecretory activity, is currently the most promising agent in the
management of severe refractory diarrhea caused by several diseases and treatments. It has been shown to be effective in the control of diarrhea associated with AIDS, carcinoid syndrome, vasoactive intestinal polypeptide (VIP) tumors, idiopathic secretory diarrhea, short-bowel syndrome and dumping syndrome (8-10). Octreotide acts directly on the epithelial cells to reduce secretion of several pancreatic and gastrointestinal hormones, including VIP, serotonin, gastrin, insulin, glucagon, growth hormone, motilin, secretin and pancreatic polypeptides (10). It prolongs the intestinal transit time and increases the intestinal absorption of fluids and electrolytes. It has also been shown to be effective in chemotherapy-induced diarrhea (CID) and is recommended for the treatment of severe diarrhea (grades 3-4) refractory to opioids, such as loperamide (10, 11). Octreotide has also been shown to be effective in diarrhea associated with graft-versus-host disease (GVHD) (12, 13).

A long-acting formulation of octreotide (octreotide LAR), consisting of microspheres of poly-DL-lactide-co-glycoside-glucose containing octreotide, has been developed, exhibiting all the properties of the short-acting subcutaneous (SC) formulation, with the additional advantage of slow drug release. To date, it has been approved for the control of chronic diarrhea associated with neuroendocrine-secreting tumors and has been evaluated in refractory chemotherapy-induced diarrhea (14-16).

In this study, the effectiveness of octreotide LAR in controlling chronic (>30 days) diarrhea refractory to high-dose loperamide and/or dietary modification (duration of therapy >48 hours), but not attributed to any medical intervention, was assessed.

Patients and Methods

Twenty-nine cancer patients (diagnosis confirmed by histology), suffering from chronic (>30 days) diarrhea, were enrolled in this study. All the patients had shown no response after 48 h of standard treatment with loperamide (4 mg p.o. as initial dose and 2 mg every 2 h or after each unformatted stool, with a maximum of approximately 12 mg/day) and/or dietary modifications. "No response" was defined as the failure of treatment to reduce the severity of diarrhea by two grades according to NCI/WHO criteria. The patients had life expectancies of at least 3 months and had not received or been scheduled to receive chemotherapy or radiotherapy or to undergo surgical operation during the 6 weeks prior to study enrollment until the end of the study. They also did not receive any concomitant antidiarrheal medication during the study and did not show hypersensitivity to octreotide. Additionally, patients with steatorrhea, renal or hepatic impairment, inflammatory bowel disease, ileus or short-bowel syndrome were excluded from the study. Patients who had received aloxigenic bone marrow transplantation within 12 months prior to study enrollment were also excluded. All patients were >18 years of age and had an Eastern Cooperative Oncology Group (ECOG) performance status score ≤2.

All the eligible patients followed antidiarrheal diet modifications and received octreotide 1.5 mg s.c. (0.5 mg, three injections daily (tid), from baseline to day 14 of the study and octreotide LAR 20 or 30 mg i.m. once every 28 days, starting from baseline, until stabilization of the effect for a week. After this time-point, the patients were gradually released from antidiarrheal diet modifications and the octreotide effect was re-evaluated after a week on a regular diet. If after 1 month of therapy (week 4) control of diarrhea was achieved, the octreotide LAR dose was reduced to 10 mg or 20 mg, according to the starting dose. If after 2 months (week 8) the control of diarrhea was maintained, an attempt to discontinue the drug was made. If not, the octreotide LAR dose was restored to the starting dose. After 3 months (week 12), the octreotide LAR dose was restored to 10 mg in the case of a recurrence of diarrhea.

All the patients were instructed to maintain diary cards with the exact time of each episode of diarrhea, the amount of stools and their texture. At specific study time-points (baseline, weeks 4, 8 and 12), the patients were asked to undergo laboratory tests which included determination of Na+, K+, total protein, albumin, hematocrit, hemoglobin and the white blood cell (WBC) count. At these time-points, all the patients were asked to perform a self-administered QOL evaluation using the Linear Analog Scale Assessment (LASA) instrument. The study was approved by the institutional ethics committee and informed consent was obtained from all participants prior to their induction into the study.

Results

A total of 29 patients were enrolled in this study. The general characteristics and demographics of the patient cohort, as well as the primary cancer site, type and duration of diarrhea and ECOG score, are summarized in Table I. All patients suffered from chronic diarrhea (mean duration 32.8 days, range 30-42; mean number of stools/day: 6.1±1.4) refractory to loperamide and at baseline received octreotide at a daily dose of 1.5 mg s.c. (0.5 mg tid) for 14 consecutive days, plus octreotide LAR at a dose of 30 mg i.m. repeated every 28 days. Furthermore, every patient followed antidiarrheal diet modifications. By week 4 (day 28), three patients (10.3%) had responded completely and their octreotide therapy was stopped, ten patients (34.5%) had partially responded (reduced stool frequency) and received octreotide LAR at a reduced dose of 20 mg i.m. thereafter and 16 patients (55.2%) continued their therapy at a dose of 30 mg i.m. By week 8 (day 56), another eleven patients had responded completely and their octreotide therapy was stopped (total number of complete responders: 14; 48.3%). Only five patients (17.2%) had not responded and their therapy was continued at a dose of 30 mg i.m., whereas ten patients (34.5%) achieved reduction of their diarrhea and continued to receive therapy at a reduced dose of 20 mg i.m. By the end of the study (week 12, day 84), the number of complete responders had increased to 23 (79.3%), while six patients (20.7%) had finally managed to control their diarrhea and continued treatment (five patients who continued octreotide LAR therapy at 30 mg i.m. until week 12, and one patient who failed to stabilize a partial response
between week 8 and week 12). Additionally, the mean number of stools per day decreased from 6.1±1.4 at baseline to 1.0±1.5 in week 12 (p<0.0005) (Figure 1).

Only five out of 29 patients (17.2%) continued to follow the antidiarrheal diet modifications, whereas 24 patients (82.8%) had returned to their regular diet by the end of the study at week 12.

The fluctuation of biochemical markers over the period of 12 weeks revealed that the mean value of sodium (Na⁺) was statistically significantly reduced from 134.7±4.4 meq/L at baseline to 140.2±5.3 meq/L at week 12 (p<0.0005). Likewise, the mean value of potassium (K⁺) at week 12 was 4.4±0.7 meq/L versus 4.1±0.7 meq/L at baseline (p=0.044). In accordance, the mean values of albumin and total protein were significantly increased from baseline to week 12. The mean value of albumin was 3.8±0.8 g/dL at week 12 versus 3.3±0.6 g/dL at baseline (p<0.0005) and the mean value of total protein was increased from 6.3±0.8 g/dL to 6.9±0.8 g/dL (p=0.002). The hemoglobin, hematocrit and WBC values showed no statistically significant changes.

All mean baseline scores for the LASA were lower than 3.3 cm on the 10-cm scale [energy level = 3.2±1.1 cm, daily activities (function level) = 3.1±1.3 cm, overall well-being (quality level) = 3.2±0.9 cm], suggesting impairment of functioning and, therefore, substantial limitations to the QOL for these patients. At week 12, all mean LASA scores had significantly increased and were above 6.0 cm [energy level = 6.2±1.4 cm (p<0.0005), function level = 6.2±1.2 cm (p<0.0005), quality level = 6.1±1.4 cm (p<0.0005)] (Figure 2).

Finally, no significant adverse effects associated with the administration of octreotide LAR were noted during the study.

**Discussion**

Diarrhea is common in cancer patients and its management represents a serious challenge to the healthcare team. Chronic diarrhea has a significant impact on the patient’s QOL,
resulting in dehydration of the patient, renal insufficiency and electrolyte imbalance and can be debilitating and potentially life-threatening. The primary goals of anti diarrheal therapy are to reduce the pain and discomfort associated with excessive bowel movements, and eliminate the need for oral or i.v. rehydration, electrolyte replacement or hospitalization. In some patients, diarrhea may be controlled by conventional treatments such as diet, bowel rest, hydration and standard anti diarrheal therapy with opioid agents, such as loperamide.

Octreotide and long-acting octreotide (octreotide LAR) have been evaluated for the treatment of diarrhea associated with carcinoid syndrome and refractory chemotherapy-induced diarrhea (CID) (7, 15-17). In one study (15), octreotide LAR 30 mg appeared to be effective for the control of loperamide-refractory chemotherapy-induced diarrhea and for the prevention of further episodes of diarrhea following continuation of the chemotherapy.

In this study, 29 patients had chronic (>30 days) diarrhea not associated with any cancer treatment-related diarrhea and refractory to loperamide, who were treated with octreotide LAR i.m. from baseline to week 12 together with octreotide s.c. for the first 14 days. The results revealed that the majority of patients (79.3%) responded well with resolution of diarrhea, while the remaining patients achieved adequate control by receiving octreotide LAR at a dose of 30 mg. The persistence of diarrhea may cause dehydration and malnutrition, leading to electrolyte and protein imbalances. Patients increased their Na+ and K+, as well as their albumin and total protein values, while under treatment with octreotide LAR.

The evaluation of the LASA questionnaires for energy, functioning and QOL revealed that the patients experienced a significant improvement in their QOL, on controlling their diarrhea.

In this study, it was demonstrated that octreotide LAR effectively controlled chronic loperamide-refractory diarrhea not associated with any medical intervention. Octreotide LAR offers the convenience of once-a-month injection in contrast to the three daily s.c. injections of octreotide, thereby improving patient compliance to treatment. The vast majority of patients controlled and finally resolved their diarrhea by receiving octreotide LAR at a starting dose of 30 mg and then at a reduced dose of 20 or 10 mg. Octreotide LAR was quite safe and no side-effects were noted during the study. The cost of octreotide may be considered a serious impediment for its application in clinical practice, but compared to the cost of hospitalization, or prolongation, it is actually low.

In conclusion, octreotide LAR is highly effective in the control and resolution of chronic loperamide-refractory diarrhea, not attributed to any medical intervention, and also appears to offer the greatest convenience and least toxicity, avoiding hospitalization and leading to an improvement in the patient’s QOL. Further studies are needed to verify the present results.

References


Received January 13, 2006
Accepted March 10, 2006