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Randomized Trial of Loperamide Versus Dose Escalation of Octreotide Acetate for Chemotherapy-Induced Diarrhea in Bone Marrow Transplant and Leukemia Patients

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This study compares maximal daily doses of loperamide to escalating doses of continuous intravenous (CI) octreotide acetate in bone marrow transplant (BMT) and leukemia patients.

Following chemotherapy, BMT and leukemia patients who developed ≥600 ml of stool volume in a 24-hr period were randomized to receive loperamide 4 mg po q6h or octreotide 150 μg mixed in hyperalimentation solution or normal saline and administered CI. Patients were assessed at 48 hr intervals for decrease in stool volume from baseline. Complete response (CR) was defined as ≥50% from baseline stool volume (BSV). Patients receiving octreotide who did not achieve a CR at 48 hr were dose escalated by doubling the dose to a maximum of 2,400 μg with evaluations at 48 hr intervals. Patients receiving loperamide who did not achieve a CR at 48 hr had treatment discontinued.

A total of 36 patients were enrolled in the study. Of these, all were evaluable for intention to treat, and 31 were evaluable for initial response. Based on intent to treat at the initial 48 hr, patients receiving loperamide had a higher complete response rate (86% vs. 45%, $P = 0.033$) than did those who received octreotide. By treatment analysis (patients who actually received the drug), patients receiving loperamide had a higher complete response rate (92% vs. 56%, $P = 0.0448$) than did those who received octreotide at the 150 μg dosage level. Additional octreotide patients eventually achieved a CR at a higher dosage level (78%).

Loperamide at maximal doses of 4 mg po q6h is more effective than octreotide 150 μg CI in treating diarrhea following chemotherapy in BMT and leukemia patients. Higher doses of octreotide may be required in a significant number of patients not responding to lower doses. © 1995 Wiley-Liss, Inc.

Key words: loperamide, bone marrow transplant, dose escalation, octreotide acetate

INTRODUCTION

Diarrhea is a frequent complication following intensive preparative regimens for patients undergoing bone marrow transplant (BMT) or induction chemotherapy regimens in leukemia patients [1]. Gastrointestinal toxicities, including severe diarrhea, are associated with increased morbidity, may prolong length of hospitalization or become life-threatening [2–4]. In these patients, diarrhea is most often secretory in nature and associated with a myriad of causes, including chemotherapy or radiotherapy, graft-versus-host disease (GVHD), antibiotics, or infection [5]. There is wide interpatient variability in the onset and severity of diarrhea, as well as response to treatment. Treatment for secretory diarrhea is symptomatic with electrolyte replacement and antidiarrheals such as loperamide, diphenoxylate/atropine, and more recently octreotide acetate, a synthetic somatostatin analogue. Lopera-

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mide slows intestinal motility via a direct effect on the nerve endings and/or the intramural ganglia of the intestinal wall. Octreotide acetate inhibits insulin, glucagon, growth hormone, and gastric acid secretion; decreases intestinal blood flow and motility; and increases large bowel water and electrolyte reabsorption [6].

Dosing and dosing schedules as well as response rates to loperamide or diphenoxylate/atropine vary and are not well defined [7]. Because these antidiarrheals are only administered orally, compliance may be problematic due to severe mucositis or nausea and vomiting. Alternatively, octreotide acetate is administered subcutaneously or intravenously by intermittent or continuous infusion. Small studies and case reports note response rates as high as 90% in patients treated with octreotide acetate for secretory diarrhea, including chemotherapy or radiotherapy induced diarrhea, and for GVHD [7–20]. Effective doses of octreotide acetate to treat secretory diarrhea are not well established and have ranged from 100 to 3,600 μg/day. We report our results comparing maximal daily doses of loperamide to escalating doses of continuous intravenous infusion octreotide acetate in BMT and leukemia patients with secretory diarrhea.

MATERIALS AND METHODS

Patient Population

From February 1993 through July 1993, patients at least 18 years old receiving intensive chemotherapy as induction therapy for leukemia or preparation for BMT were eligible for monitoring of diarrhea and given the option to participate in the study. Written informed consent was obtained in patients willing to participate prior to the development of diarrhea in order to avoid treatment delay. Participating patients saved their stool, which was measured and recorded daily. When stool volume reached ≥600 ml within 24 hr, patients were enrolled and randomized to either octreotide or loperamide as described below. Patients with positive stool cultures for *Shigella*, *Salmonella*, *Campylobacter*, or parasites were excluded. Patients who had received antidiarrheal treatment less than 24 hr before enrollment were excluded. Patients were permitted to withdraw consent at any time. Pretreatment laboratory evaluation included a complete blood count, biochemistry profile (consisting of sodium, potassium, blood urea nitrogen, serum creatinine, total protein, albumin, total bilirubin, serum glutamic-oxaloacetic and glutamic-pyruvic transaminases) and stool studies (*Salmonella*, *Shigella*, *Campylobacter*, fecal leukocytes, *Clostridium difficile* toxin, ova, and parasite). A complete blood count and biochemistry profile were obtained at least three times weekly and stool cultures at least twice weekly.

Prior to initiation of study drug, stool was cultured for *Clostridium difficile* by toxin analysis. Results were available a minimum of 48 hr after culture was sent. Treatment was not delayed pending culture results; therefore, patients with stool cultures positive for *Clostridium difficile* were initially treated and included in the intent to treat analysis. Once positive culture results were available, appropriate therapy was initiated, and the patient was withdrawn from the study.

Response Criteria

Baseline stool volume was defined as the total 24-hr stool volume prior to enrollment. Stool volume was recorded in 8-hr shifts and totalled every 24 hr. Response to antidiarrheal treatment was assessed at 48-hr intervals. Control of diarrhea was graded as major response (greater than or equal to 50% decrease from baseline stool volume over last 24 hr), minor response (20–49% decrease from baseline stool volume over last 24 hr), and no response (less than 20% decrease from baseline stool volume over last 24 hr).

Treatment Design

The treatment sequence was computer generated (Epistat, Round Rock, TX) employing simple randomization. Patients randomized to octreotide (Sandoz Pharmaceuticals, East Hanover, NJ, lot# 006T1287) initially received 150 μg administered intravenously over 24 hours in hyperalimentation solution. Patients not receiving hyperalimentation received octreotide intravenously over 24 hr in 250-ml normal saline. This dose and schedule was continued for 48 hr. After 48 hr, the dose of octreotide was doubled in patients who had a minor or no response. The octreotide was then doubled every 48 hr to a maximum of 2,400 μg if patients continued to have a minor or no response despite dose increase. Patients still not exhibiting a major response after 48 hr at 2,400 μg were withdrawn from the study and given alternative treatment. When major response was achieved on octreotide, patients continued on that dosage level until stool was nonliquid for 24 hr or no stool output for 48 hr. Patients randomized to loperamide (Vangard Laboratories, Glasgow, KY, lot# 0362002) received 4 mg po q6h for 48 hr. Patients were withdrawn from the study and given alternative treatment if they had a minor or no response at the first 48 hr evaluation. Patients exhibiting a major response on loperamide continued 4 mg po q6h until nonliquid stool for 24 hr or no stool output for 48 hr.

Statistical Analysis

The primary endpoint of the study was major response at 48 hr. Secondary endpoints included the category of response (major, minor, or none) and, for the patients randomized to octreotide, the dose at which major response was achieved. All patients were included in the primary analysis based on the intention to treat principle [21]. The primary endpoint was analyzed using Fisher's

TABLE I. Patient Enrollment Information

Enrollment information	No. of patients		P
	BMT	Leukemia	
Total population	52	43	—
Never approached for informed consent	5	8	0.13
Approached for informed consent	50	32	—
Refused to consent	14	4	0.61
Consented to enroll in study if eligible	36	28	
diarrhea <600 ml in a 24-hr period	12	7	0.28
diarrhea ≥600 ml and randomized	21	15	
refused/unable to enroll once eligible	3	6	0.47

exact test [22]. The secondary endpoint of category of response was analyzed using a test for a trend in proportions [22]. The sample of the study was determined using the method of Cassagrande, Pike, and Smith [23,24].

The minimum sample size for each group was 14 patients. With this sample size, a test of equality for two proportions with a type I error rate of 0.05 has 70% power to detect a difference in response rates of 0.10 vs. 0.60. It was thought that any difference smaller than this would not justify recommending a treatment plan that could be more expensive and more technically difficult.

RESULTS

Patient Characteristics

Eighty-two BMT and leukemia patients were approached for consent to participate in the study. Patient enrollment information is shown in Table I. Sixty-four patients (36 BMT and 28 leukemia) consented to participate in the study. Thirty-six patients (21 BMT and 15 leukemia) were enrolled in the study after developing ≥600 ml of diarrhea (liquid stool) within 24 hr. Of these 21 BMT patients, 3 received an allogeneic transplant, and 18 underwent an autograft. Of the 3 who underwent allografting, diarrhea occurred on day 10 (2 patients) and on day 11 (1 patient); none of these 3 patients had any clinical signs consistent with GVHD; therefore, the occurrence of diarrhea was most consistent with being chemotherapy induced. Nineteen patients (12 BMT and 7 leukemia) did not develop diarrhea ≥600 ml in a 24 hr period. Nine patients (3 BMT and 6 leukemia), although eligible and consent obtained, did not enroll in the study due to requests by the patient for treatment before 600 ml stool output (5), inability to quantify stool (2), non-compliance with oral medications (1), and one patient not receiving hyperalimentation (before amendment to protocol to administer octreotide by continuous intravenous infusion if not on hyperalimentation). The rates at which BMT and leukemia patients were invited for participation, gave informed consent, became eligible for the study, and withdrew consent were not statistically significantly different between the two patient populations.

Characteristics of patients are shown in Table II. The distributions between the two treatment arms of sex, age, diagnosis, and chemotherapy regimen (classified as BMT preparative or leukemia cytoreductive) were not statistically significantly different. Fourteen patients were randomized to receive loperamide and 22 patients were randomized to receive octreotide. All 36 patients were evaluable for intention to treat (management strategy). One patient did not receive loperamide for the 48-hr evaluation period due to difficulty swallowing. Four patients did not receive octreotide for the 48-hr evaluation period due to lost IV access (1), drug not administered (1), infusion pump malfunction (1), and failure to quantitate stool (1). Therefore, these five patients were not included in the evaluation for initial response to antidiarrheal treatment (treatment analysis).

Six patients did not have baseline stool studies performed at the time of study enrollment. Of the thirty patients with baseline stool studies, three (2 LOP, 1 OCT) were positive for *Clostridium difficile* by toxin analysis. In all three patients, study drug was initiated prior to stool study results. One of the three patients did achieve a major response at 48 hr on the loperamide arm. Five of the six patients who did not have baseline stool studies achieved a major response at the first 48 hr evaluation point.

The mean number of days to diarrhea onset from the time chemotherapy was initiated was 9.5 days in the loperamide group and 10.7 days in the octreotide group.

Response to Treatment

Of the 13 patients who received loperamide, twelve patients achieved a major response at 48 hr. One patient did not respond to treatment and was later withdrawn from study for positive stool *Clostridium difficile* toxin.

Eighteen patients received octreotide; 10 achieved a major response at 48 hr, six a minor response, and two no response. One patient who did not respond to treatment was later withdrawn from study for positive stool for *Clostridium difficile* toxin. Of the six patients with a minor response at the 150-μg dosage level, four patients achieved a complete response once escalated to a higher dosage level (1 at 300μg, 2 at 600μg, and 1 at 1,200μg). One patient had a minor response at the 2,400-μg dosage level and one patient failed to respond, despite dosage level. The other patient with no response at 48 hr was later withdrawn from study due to octreotide infusion cessation. Because simple randomization was employed, the number of patients in the octreotide arm was larger than in the loperamide arm. Response to treatment is summarized in Tables III and IV.

Based on the intent to treat analysis (management strategy), 12 of the 14 loperamide patients (86%) achieved a major response at the first 48-hr evaluation period versus 10 of the 22 octreotide patients (45%, $P = 0.033$). By

TABLE II. Patient Characteristics

Characteristic	Value		P
	Octreotide	Loperamide	
No. enrolled	22	14	
No. evaluable for intent to treat	22	14	
No. evaluable for initial response	18	13	
Male	11	8	0.74
Female	11	6	
Age			
Mean	48	45	
Range	30–65	26–68	
Diagnosis			
Acute myelocytic leukemia	12	6	0.73
Non-Hodgkin's lymphoma	3	3	
Breast cancer	4	1	0.83
Multiple myeloma	1	2	
Chronic myelocytic leukemia	1	1	
Acute lymphocytic leukemia	0	1	
Myelodysplastic syndrome	1	0	
Chemotherapy regimen			
BMT preparative regimen	14	7	0.50
Busulfan, cyclophosphamide, etoposide	3	5	
Busulfan, cyclophosphamide, cytarabine	5	0	
Cyclophosphamide, thiotepa, carboplatin	4	1	
Busulfan, cyclophosphamide	1	1	
Busulfan, cyclophosphamide, diaziquone	1	0	
Leukemia cytoreductive	8	7	
Etoposide, mitoxantrone, cytarabine	7	5	
Idarubicin, cytarabine	1	1	
Cytarabine, mitoxantrone	0	1	

TABLE III. Treatment Outcome at First 48-hr Evaluation Period

Response	Octreotide (150 μg/24 hr)	Loperamide (4 mg po q6h)	P
Intent to treat analysis	22	14	
Complete response	10	12	0.033
PR, NR, or no treatment	12	2	
Treatment analysis	18	13	
Complete response	10	12	0.0448
PR, NR	8	1	

treatment analysis (patients who actually received the drug), 12 of 13 loperamide patients (92%) achieved a major response versus 10 of 18 octreotide patients (56%, $P = 0.0448$) at the first 48-hr evaluation. When the dose escalation of octreotide is included, 14 of the 18 octreotide patients (78%) eventually achieved a major response with octreotide.

There were no major adverse events reported for either treatment arm. Two patients on the octreotide arm (one 150μg, one 300 μg) had mild elevations in total bilirubin which completely resolved following completion of study drug. One patient receiving octreotide experienced abdominal cramping and flatulence, which ceased following early discontinuation (before first 48-hr evaluation period) of drug.

The costs of the two treatments were compared. The average wholesale price (AWP) for 24 hr of treatment with loperamide 4 mg po q6h was $4.36. The AWP for 24 hrs of octreotide 150μg was $11.34 (this does not include intravenous administration costs).

DISCUSSION

Diarrhea is a prominent feature of chemotherapy-related gastrointestinal toxicity associated with BMT preparative regimens and leukemia induction treatment. With the current use of myeloid growth factors to decrease the severity and duration of myelosuppression, gastrointestinal toxicities are often a major cause of treatment-related morbidity, which can significantly prolong the length of hospitalization. There were two goals to the design of this trial: (1) to determine the most efficacious intravenous dose of octreotide in patients undergoing intensive chemotherapy, and (2) to compare the results of octreotide to loperamide in a randomized clinical trial for this patient population.

Patients randomized to receive octreotide started at a dose of 150 μg administered intravenously over 24 hr in either the hyperalimentation solution or normal saline. Ten patients achieved a major response after 48 hr of therapy, while six achieved a minor response. Of these

TABLE IV. Treatment Outcome for Octreotide Failures at 150μg

	Octreotide (n = 6)[a]				
Response	300 μg	600 μg	1,200 μg	2,400 μg	Total
Complete response	1	2	1	0	4
Partial response	0	0	0	1	1
No response	0	1	0	0	1

[a]Of the seven patients who did not respond at 150 μg, six were dose escalated and one patient did not receive further therapy.

six minor responders, four achieved a major response at higher doses of octreotide. Previous trials evaluating the efficacy of octreotide for treatment of secretory diarrhea have used daily doses ranging from 100 to 750 μg. Cascinu et al. [7] used a dose of 100 μg sc bid and achieved a 90% CR in patients with 5-fluorouracil-induced diarrhea. In a group of 11 patients with refractory diarrhea associated with 5-FU and/or pelvic radiotherapy, all patients responded to a dose of 50 μg sc bid. In a small group of 4 patients receiving HLA-compatible allogeneic bone marrow for hematologic malignancies, octreotide was escalated to a dose of 100 μg sc tid [16]. Response was variable, but the treatment course was complicated by GVHD-associated diarrhea. In another small group, of six patients receiving octreotide for documented GVHD-associated diarrhea, doses ranged from 100 μg sc bid to 250 μg tid [14]. Even though the majority of our patients randomized to receive octreotide responded at the initial dose, there is a dose-response relationship, with most (78%) patients responding at doses up to 600 μg/24-hr period.

Since all patients had central venous access and were severely thrombocytopenic, and to avoid any pain associated with subcutaneous injections, octreotide was given as a continuous infusion either in hyperalimentation solution or in normal saline. There has been concern regarding whether octreotide can be given with hyperalimentation. It is known that glycosylation occurs when proteins such as albumin or octreotide are added to hyperalimentation or high-dextrose-containing solutions (e.g., Sandostatin, Sandoz, per package insert). In addition, glycation has been found to occur in a variety of proteins in diabetic patients in vivo [25]. There has been nothing documented in the literature to support any loss of effect or potency of octreotide as a result of this glycosylation. In addition, Ritchie et al. [26] studied the activity of octreotide in hyperalimentation at room temperature for 48 hr and for 7 days under refrigeration and found that octreotide was physically compatible with hyperalimentation during this time period with the conditions as stated. It has been routine policy at our institution to mix octreotide with hyperalimentation solution, and a difference in response between octreotide administered subcutaneously in three divided doses versus continuously in hyperalimentation has not been apparent.

Dosing and dosing schedules of loperamide vary; the dose of loperamide chosen in this randomized trial was the maximum recommended dose of 4 mg q6h. When one considers either the intent to treat or the treatment analysis at 48 hr, the treatment group receiving loperamide had significantly more major responders. If one chooses to include the patients who responded to higher doses of octreotide, response rates are more equivalent between the two arms; however, the cost of octreotide is significantly higher than the cost of loperamide. In the only other randomized trial with octreotide versus loperamide in the treatment of fluorouracil-induced diarrhea, the dose of loperamide was 2 mg q6h, which may, in part, explain the inferior results with loperamide compared to the octreotide-treated patients [7]. In this trial of aggressively treated patients, both the loperamide and octreotide were well tolerated. Despite most patients experiencing mucositis or stomatitis secondary to their treatment regimen, only one patient was unable to tolerate oral medication and could therefore not receive loperamide. Although all patients on the octreotide arm had intravenous access at initiation of treatment, two patients were unable to complete treatment for the first 48-hr period due to circumstances related to the intravenous line (lost IV access and infusion pump malfunction). These two patients were unable to receive further octreotide therapy.

For patients undergoing intensive chemotherapy for bone marrow transplantation or for leukemia induction therapy, diarrhea continues to be a major problem. In this randomized study we found loperamide at a dose of 4 mg q6h to be effective in the treatment of bone marrow transplant and leukemia patients with chemotherapy-induced diarrhea. It is important to emphasize that of the 21 BMT patients, all received a chemotherapy-based preparative regimen and only three received allografts; therefore, the potential role of loperamide or octreotide for patients experiencing diarrhea in total body irradiation-based preparative regimens or allogeneic BMT has not been adequately assessed in this trial. Although octreotide at a dose of 150 μg/24-hr infusion was not as effective as loperamide, a higher dose of 600 μg/24-hr infusion

would be more effective and should be the optimal initial dose of octreotide in this patient population. Loperamide is less expensive and can be administered orally. Octreotide may be used as an alternative for those patients who are unable to tolerate oral medications or for those patients who do not respond to loperamide.

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