Original Article

Effectiveness and Tolerability of Amidotrizoate for the Treatment of Constipation Resistant to Laxatives in Advanced Cancer Patients

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Abstract

Context. Constipation is a common problem for advanced cancer patients, and is generally inadequately treated.

Objectives. The aim of this study was to prospectively evaluate the effectiveness and tolerability of amidotrizoate (AM) in patients unresponsive to current laxatives.

Methods. A consecutive sample of advanced cancer patients was surveyed. Inclusion criteria were no bowel movements for three days despite receiving regular doses of senna or lactulose. AM 50 mL was administered orally; the dose could be repeated the day after, based on clinical judgment and/or patients' preference. Age, sex, primary tumor, previous abdominal surgery, chemotherapy and radiotherapy performed in the previous month, and the use of opioids were recorded. Nausea, the presence of early satiety, and fluid and food intake also were measured. Time to first bowel movement was recorded, and adverse effects attributable to AM.

Results. Ninety-nine patients were surveyed (36 women/63 men). The mean age was 65.7 years (SD ± 12.2) and the mean Karnofsky score was 46.8 (SD ± 9.4). Patients had no bowel movement for a mean of four days (SD ± 1.8, range 3–15 days). A total of 80.8% of patients were receiving opioids in doses of mean daily oral morphine equivalents of 164 mg (SD ± 235). After AM administration (mean 9.9 ± 6.5 hours), 44.4% of patients had a bowel movement within 24 hours. This effect was associated with significant improvement of other symptoms and was independent of age ($P = 0.513$), gender ($P = 0.090$), Karnofsky status ($P = 0.979$), days of constipation ($P = 0.198$), concomitant chemotherapy ($P = 0.098$) or radiotherapy ($P = 0.414$), the use of opioids ($P = 0.361$), opioid doses ($P = 0.420$), and primary tumor ($P = 0.231$). The treatment was more effective in patients who had previous abdominal surgery (HR = 3.33).

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Conclusion. AM was found to be an easy and inexpensive breakthrough medication to induce a bowel movement in about 45% of advanced cancer patients not responsive to common laxatives, with limited and acceptable adverse effects. J Pain Symptom Manage 2011;41:421–425.

Key Words
Constipation, opioids, cancer patients, amidotrizoate

Introduction

Constipation is a common problem for patients with advanced cancer. It can generate considerable suffering for patients because of both unpleasant physical symptoms and psychological preoccupations that can arise. In addition to causing discomfort, constipation affects daily living, nutritional intake, and socialization, thus compromising quality of life. Untreated constipation may progress to obstipation, which may potentially lead to life-threatening complications associated with bowel obstruction.[1] Although the pathogenesis is multifactorial, including dietary, mobility, and disease factors, opioid drugs play a prominent role. Indeed, constipation is considered the first cause of adverse drug reactions in hospitalized oncology patients.[2]

The prevalence of constipation among all patients taking opioids ranges from 50% to 100%.[3] Constipation in most patients is generally inadequately treated. Although a survey in the UK showed that, for 75% of patients, no change in the perception of constipation was observed and severity of constipation was overestimated by nurses,[4] in an analysis of randomized comparative trials, all the laxatives demonstrated a limited level of efficacy and a significant number of patients required rescue treatments.[5]

The literature about the use of laxatives by palliative care units shows that appropriate doses of laxatives are not commonly administered.[4] Moreover, a combination of drugs acting with different mechanisms is only minimally reported.[3] This topic remains controversial because there is no scientific evidence on the treatment of constipation.

Recently, an expert working group produced clinical practice recommendations on the management of constipation in palliative care. After inadequate management with traditional laxatives, including a softener and a stimulant, recommendations suggest second- and third-line treatments, including rectal suppository or enema, and manual evacuation, respectively.[6] Enemas, besides being stressful, have some potential to cause intestinal perforations. These maneuvers, particularly manual interventions, are highly stressful and troublesome for both patients and personnel.

In recent years, we have been successfully using amidotrizoate (AM), a hyperosmolar water-soluble contrast medium, as a second-line treatment. It is an anionic, bitter-flavored mixture of sodium diatrizoate, meglumine diatrizoate, and a wetting agent, polysorbate 80.[7] This substance has been used for diagnostic purposes and as a first attempt to early resolve a potentially reversible condition of malignant bowel obstruction. In combination with other agents, it has been found to be effective in the recovery of bowel transit in most patients.[8]

The aim of this study was to prospectively evaluate the effectiveness of AM in patients unresponsive to current laxatives. The secondary outcome was to assess the tolerability of this agent.

Patients and Methods

All consecutive cancer patients admitted during a period of one year to an acute pain relief and palliative care unit were surveyed. Inclusion criteria were no bowel movements for three days despite receiving regular doses of senna or lactulose (four pills/day of senna or four spoons/day of lactulose, or a combination of both). Informed consent and ethical committee approval were obtained. Patients with a short life expectancy (less than two weeks), spinal compression, or clear signs of

bowel obstruction were excluded. All patients were hydrated intravenously with a minimum of 800 mL/day of electrolyte solution; 50 mL of AM were administered orally, leaving the option of a repeat dose the day after, based on clinical judgment and/or patient's preference (e.g., to avoid an enema).

Age, sex, primary tumor, previous abdominal surgery, chemotherapy and radiotherapy performed in the previous month, and the use of opioids were recorded. Nausea (using a scale from 0 to 3, corresponding to "not at all," "slight," "a lot," and "severe," respectively), and the presence of early satiety were also recorded. Reduction of fluid and food intake was measured by using a scale from 0 to 3, corresponding to "not at all," "slight," "a lot," and "very much," respectively. Time to first bowel movement was recorded, and adverse effects attributable to AM. In case of diarrhea, basal laxatives were discontinued and were started again after diarrhea resolved.

The primary outcome of this study was to evaluate the percentage of patients who had a bowel movement within 24 hours after administration of AM. The secondary outcome was to evaluate the tolerability of this agent.

Statistical Analysis

All continuous data were expressed as a mean ± standard deviation (SD) of the mean. Pearson's Chi-squared test and Fisher's exact test were used to compare the frequency of AM efficacy vs. gender, primary tumor, previous abdominal surgery, chemotherapy and radiotherapy performed in the previous month, early satiety, and adverse effects. One-way analysis of variance and the Mann-Whitney *U* test were performed to compare the AM efficacy with the parametric (age, opioid doses, constipation days) and nonparametric (Karnofsky score, nausea, fluid reduction, food intake) variables. The paired Wilcoxon signed-rank test was used to compare symptom intensity at the different time intervals. The relation between effect of AM on the bowel movement and age, Karnofsky status, days of constipation, use of opioids, and opioid doses was performed using a linear regression model. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for gender, primary tumors, previous abdominal surgery, chemotherapy, or radiotherapy using a multiple logistic regression model. All *P*-values were two-sided, and *P*-values less than 0.05 were considered statistically significant. Data were analyzed by the Epi Info software, version 6.0 (Centers for Disease Control and Prevention, Atlanta, GA) and SPSS Software, version 14.0 (SPSS Inc., Chicago, IL).

Results

Of the 495 patients admitted in one year, 106 patients presenting with the inclusion criteria were recruited for the study. Seven patients were excluded because of their short life expectancy and 99 were finally surveyed. Patient characteristics are described in Table 1. Patients were constipated for a mean of four days (SD ± 1.8, range 3–15 days). A total of 80.8% (80 of 99 patients) were receiving opioids in doses of mean daily oral morphine equivalents of 164 mg (SD ± 235). Twenty-three patients had a previous surgery; 29 and 3 patients had received chemotherapy or radiotherapy in the last month, respectively.

Forty-four patients (44.4%) had a bowel movement within 24 hours after AM administration (mean 9.9 ± 6.5 hours). This effect was associated with significant improvement in nausea, hydration, and nutrition observed (Table 2). Significant improvements also were observed for early satiety ($P < 0.048$). Forty-five patients who did not respond to AM received an enema, two of whom responded within the next 24 hours. After a new dose of AM (14 patients), seven responded positively.

Table 1
Patient Characteristics

No. of patients	99
Age, mean (±SD)	65.7 (12.2)
Karnofsky score, mean (±SD)	46.8 (9.4)
Constipation days, mean (±SD)	4.0 (1.8)
Opioid doses (in mg oral morphine equivalents), mean (±SD)	164 (235)
Gender (M/F), *n*	63/36
Previous surgery, *n*	23
Previous chemotherapy, *n*	29
Previous radiotherapy, *n*	3
Primary tumor, *n*	
Lung	30
Genitourinary	19
Gastrointestinal	11
Breast	8
Pancreas	8
Head and neck	6
Other	17

Table 2
Nausea and Fluid and Food Intake in Patients Who Had a Bowel Movement Within 24 Hours After Administration of AM

	T0	T1	T2	*P*
Nausea (0–3)	0.63 (0.9)	0.40 (0.7)	0.28 (0.6)	0.018
Hydration	1.28 (0.8)	0.97 (0.7)	0.88 (0.7)	0.005
Nutrition	1.49 (0.7)	1.09 (0.7)	0.94 (0.7)	0.003

Data are expressed as a mean (SD).

The effect of AM on bowel movement (according to linear regression analysis) was independent of age ($P = 0.513$), Karnofsky status ($P = 0.979$), days of constipation ($P = 0.198$), and the use of opioids ($P = 0.361$) and opioid doses ($P = 0.420$). Moreover, according to multiple logistic regression analysis, the effect of AM on bowel movement was independent of gender ($P = 0.090$), primary tumor ($P = 0.231$), concomitant chemotherapy ($P = 0.098$), or radiotherapy ($P = 0.414$). The treatment was more effective in patients who had received abdominal surgery (HR = 3.33; 95% CI: 1.18, 9.40; $P = 0.037$) (Table 3).

Twenty-nine patients reported adverse effects related to study medication (Table 4). As expected, the most frequent adverse effect (19 patients) was diarrhea. These effects were limited in time and spontaneously diminished without specific intervention. Laxatives could be started again within 48 hours.

Discussion

Patients at admission to an acute palliative care unit may have many factors contributing to constipation, including dehydration, metabolic changes, and concurrent medications. Patients who suffer from severe constipation despite laxative treatment may frequently require some intervention. In the literature, the use of breakthrough medications for constipation resistant to common laxatives has been seldom assessed. Current recommendations by a pan-European working group suggest second- and third-line treatments, including rectal suppository or enema, and manual evacuation, respectively.[6] These maneuvers are universally considered as a last resort because they are uncomfortable for patients, particularly manual interventions.

Table 3
Multiple Logistic Regression Analysis of AM Efficacy vs. Gender, Primary Tumor, Previous Abdominal Surgery, Chemotherapy, or Radiotherapy

	Hazard Ratio (95% Confidence Interval)	*P*
Gender	0.484 (0.21, 1.12)	0.090
Primary tumor	2.571 (0.53, 12.37)	0.231
Abdominal surgery	3.333 (1.18, 9.40)	0.037
Chemotherapy	1.963 (0.79, 4.85)	0.098
Radiotherapy	0.440 (0.03, 5.02)	0.414

Table 4
Adverse Effects Related to the Study Medication

Diarrhea	19
Vomiting	2
Colic	8
Rumbling	1
Soft feces	2
Abundant feces	3
Fecal incontinence	1

Some patients had more than one adverse effect.

In this study, AM was effective and well tolerated as it induced a bowel movement within a mean of 10 hours in about 45% of patients who were regularly receiving laxatives unsuccessfully. This means that about half of patients who are severely constipated despite the use of laxatives may avoid invasive and uncomfortable measures, such as an enema or manual evacuation. AM also was fairly well tolerated in terms of palatability; it has the flavor of anise. Moreover, symptoms associated with constipation, such as nausea, early satiety, and fluid and food intake, significantly improved. Adverse effects were acceptable and self-limited, with less than 20% of patients developing diarrhea, ceasing spontaneously within 24 hours.

This effect was obtained regardless of age, gender, Karnofsky status, days of constipation, oncological treatments, and the use of opioids and their doses. Of interest, the treatment seemed to be more effective in patients with a previous surgery. It could be supposed that the use of AM may help patients with postsurgical adherence.[7] This observation deserves further investigation.

Studies on the use of laxatives are limited and often of poor quality, due to the low number of patients accrued, and differences in laxatives and doses. In all the studies examined, laxatives given chronically often required rescue laxatives and no agent was found to be superior to another one.[5] Moreover, no information exists on the use of rescue laxatives in circumstances where laxatives given daily to prevent or limit constipation are ineffective. According to the

results of the present study, AM could represent a good alternative to unpleasant procedures. Recently, peripherally acting mu-antagonists have been designed to block the peripheral effects of opioids while sparing central analgesia. Methylnaltrexone, given as breakthrough medication, can reverse opioid-induced constipation by enhancing laxation within four hours in about 50% of patients. Common adverse effects experienced included abdominal cramping and flatulence.[9] Costs may be of concern and future comparative studies should provide more information about the cost-effectiveness of these breakthrough treatments.

In conclusion, AM was found to be an easy and inexpensive means to induce a bowel movement in about 45% of advanced cancer patients who suffer from severe constipation despite laxative treatment, with limited and acceptable adverse effects. Data should be considered with caution, as the study may have some limitations. This was an observational, open-label, prospective study providing preliminary information on the use of a rescue treatment in advanced cancer patients resistant to laxative drugs, and no comparison with other treatments was performed. Senna and lactulose were the laxative medications used before administering AM. These are the most common laxative drugs used in Italy, alone or in combination, and doses administered were in the range of the department policy, reflecting common clinical practice. We also considered an arbitrary time of three days to define a constipation resistant to laxatives. This seems to be a reasonable timing before starting an alternative intervention. Finally, the study was performed in a specific setting, that is, an acute palliative care unit where admitted patients are not necessarily at the end of life and may still receive anticancer therapies. Further studies with an appropriate design could provide more data on the use of rescue medications in patients resistant to laxatives given chronically.

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