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Midazolam for acute emesis refractory to dexamethasone and granisetron after highly emetogenic chemotherapy: a phase II study

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Abstract *Goals of the work:* To assess whether the addition of midazolam to dexamethasone and granisetron could ameliorate the refractory acute nausea and/or vomiting caused by a highly emetogenic platinum-based chemotherapy. *Patients and methods:* Enrolled in the study were 30 consecutive adult patients with refractory acute emesis. Nausea and vomiting were assessed by physicians and graded according to the NCI common toxicity criteria. Nausea was further self-assessed by patients using a visual analogue scale. Statistical analysis was performed by nonparametric tests. *Results:* With the introduction of midazolam, 73% of patients had a reduction of at least one grade in nausea and vomiting intensity in comparison with the previous cycle of chemotherapy. From the second cycle, six patients (23%) had complete control of acute vomiting, a benefit that usually persisted in the subsequent cycles. Five more patients achieved complete control of acute vomiting during the third course; this effect persisted in the subsequent courses as well. The average relative reduction in acute nausea and vomiting grade from the first to the second course was 48% (95% CI 34–62%) and 48% (95% CI 31–65%), respectively. A significant difference in acute nausea and vomiting over all the six courses of chemotherapy administered was recorded (Friedman ANOVA, P <0.0001). Comparing each course with any subsequent course, a significant reduction in acute nausea and vomiting was observed between the first and second course, the first and third course, and the first and fourth course. *Conclusions:* Our results suggest that midazolam may be a useful adjunct to standard antiemetic drugs for patients receiving highly emetogenic cisplatin-based chemotherapy. A randomized trial is warranted to confirm these results.

Keywords Midazolam · Chemotherapy · Emesis

Introduction

Nausea and vomiting during chemotherapy are a challenging issue for a large number of patients since these symptoms may compromise their quality of life and compliance with chemotherapy schedule, and consequently the dose intensity [1]. Nausea and vomiting have a considerable impact on all aspects of life of these patients, and their family and caregivers. The distress resulting from these symptoms can escalate over time [2, 3] and potentially lead to the patient's withdrawal from the most effective antineoplastic therapy. In fact, failing to control these side effects can lead to a delay in or refusal of a possibly life-saving therapy in 25–50% of patients [4]. The combination of dexamethasone and 5-HT3 antagonists is the standard therapy for highly emetogenic chemotherapy. Complete

protection against acute emesis after cisplatin >50 mg/m^2 has been documented in 70–90% of patients [5]. Anxiety resulting from uncontrolled vomiting and the consequent visit to the cancer center may contribute to poor control by standard antiemetic regimens.

In several studies, benzodiazepines have been demonstrated to improve comfort and decrease anxiety in patients receiving cancer chemotherapy. In particular, lorazepam has been reported to be capable of reducing the severity and the duration of nausea and vomiting [6, 7]. However, its slow onset and long duration of action can result in sedation and undesirable anxiolytic effects lasting longer than necessary. Midazolam is a short-acting benzodiazepine with a rapid onset of action, which is used for induction of general anesthesia and preoperative sedation [8]. There are several reports on the antiemetic effect of midazolam for prolonged postoperative emesis resistant to the usual treatments [9]. The suggested mechanism of action of midazolam as an antiemetic is by decreasing dopamine input at the chemoreceptor trigger zone (CTZ) in addition to reducing anxiety [8]. Midazolam may also decrease adenosine reuptake [10], leading to an adenosine-mediated reduction in synthesis/release and postsynaptic action of dopamine at the CTZ [8]. Midazolam may also decrease dopaminergic neuronal activity and 5-hydroxytryptamine release by binding to the gamma-aminobutyric (GABA) benzodiazepine complex [11].

In a previous phase I study, the optimal dose of midazolam in cancer patients treated with cytotoxics drugs in an outpatient setting has been shown to be 0.04 mg/kg [12]. Based on this background, we carried out this prospective phase II study to assess whether the addition of midazolam to dexamethasone and granisetron could ameliorate the refractory acute nausea and/or vomiting caused by a highly emetogenic platinum-based chemotherapy.

Patients and methods

Patients

From January 2001 to April 2003, 30 consecutive adult patients who were receiving cisplatin-based chemotherapy (≥50 mg/m^2) and reported NCI common toxicity criteria (NCI-CTC) grade 2 acute nausea (oral intake significantly decreased) and/or vomiting (two to five episodes in 24 h over pretreatment) resistant to dexamethasone and granisetron given as single doses of 20 mg and 3 mg, respectively, were prospectively included in this study.

Four patients were not considered evaluable because they did not meet the inclusion criteria (two patients) or had incomplete information in their medical charts (two patients). Of the evaluable patients, 15 were male and 11 were female, and their median age was 58 years (range 30–70 years). The primary cancer diagnoses were urogenital (nine patients), lung (six), breast (six), and other (five). All patients received prophylaxis therapy for delayed emesis. They received dexamethasone 4 mg orally once daily for 5 days combined with 20 mg metoclopramide orally three times daily. In addition to the standard therapy for acute emesis, these outpatients received midazolam 0.04 mg/kg as a continuous infusion during the administration of chemotherapy. The median time of infusion was 4 h. At the end of treatment all patients were discharged from the day hospital.

Eligibility requirements were age >18 years, Karnofsky performance status >70%, leukocyte count >3000/μl, platelet count >100,000/μl, serum bilirubin ≤2 mg/dl, serum creatinine ≤2 mg/dl, stable heart rhythm, no active angina, and no clinical evidence of congestive heart failure or angina. All patients gave their written informed consent. Exclusion criteria were severe concurrent illness other than neoplasia (gastrointestinal occlusion, CNS metastases or hypercalcemia), concurrent abdominal radiotherapy, pregnancy, and presence of nausea and vomiting.

Response and toxicity assessment

Acute vomiting was recorded according to the following scale: *grade 0* none; *grade 1* one episode in 24 h over pretreatment; *grade 2* two to five episodes in 24 h over pretreatment; *grade 3* six or more episodes in 24 h over pretreatment or need for i.v. fluids; *grade 4* requiring parenteral nutrition, physiologic consequences requiring intensive care, or hemodynamic collapse. The absence of emetic episodes was defined as complete protection from vomiting. Nausea was recorded according to the following scale: *0* none; *1* mild (patient able to eat); *2* moderate (oral intake significantly decreased); and *3* severe (no significant oral intake necessitating i.v. fluid).

In addition, nausea was recorded according to a VAS (from 0, no nausea, to 10, severe nausea). The patients filled out the VAS within 24 h of chemotherapy infusion. After 24 h, the investigators called patients by phone to record as soon as possible the presence or absence of acute nausea and or vomiting, which were graded according to NCI-CTC version 2.

This information was used as a comparator with that derived from the VAS. The absence of nausea was defined as complete protection from nausea. The absence of emetic episodes was defined as complete protection from vomiting. An emetic episode was defined as a single vomit or retch, or any number of continuous vomiting episodes or retches. It was required that one emetic episode be separated from another by an absence of vomiting or retching for at least 1 min. Finally, delayed nausea and vomiting were measured only by NCI-CTC grade. Patients were observed by a nurse and an investigator during chemotherapy for sedation, nausea, and number of emetic episodes. Sedation was graded as follows: *0* none; *1* mild, patient lethargic but aroused by verbal stimuli and com-

pletely oriented to person, place and time when awakened; *2* moderate, patient aroused only by physical stimuli but completely oriented when awakened; *3* marked, patient aroused only by physical stimuli and completely disoriented when awakened.

Statistical methods

Nausea was self-assessed by patients using a VAS, and measurements were rounded to the nearest integer, thus producing an ordinal scale; nausea and vomiting were further assessed by physicians and graded according to the NCI-CTC version 2. Both measurements were not normally distributed and statistical analysis was performed using nonparametric tests. The degree of correlation between VAS scores and NCI-CTC grades were assessed using Spearman's rank order correlation. The main endpoint of the study was to assess the difference in nausea and vomiting between the first and second course of chemotherapy, that is before and after the introduction of midazolam. This was assessed using Wilcoxon's matched pairs test to compare symptom intensity and Fisher's exact test to compare the percentage of responses. The patients received up to six courses of therapy, which were fully evaluated. Non-parametric Friedman analysis of variance (ANOVA) was employed to assess the overall variations in nausea and vomiting intensities throughout all six cycles. Wilcoxon's Matched Pairs Test was used to reciprocally compare the courses of chemotherapy adopting the Bonferroni correction for multiple comparisons.

Results

The results of the self-assessment of nausea by patients using the VAS were highly correlated with its assessment by physicians using NCI-CTC grade (Spearman $R = 0.88$, $P < 0.000001$). All patients experienced grade 2 acute nausea and grade 2/3 acute vomiting with the first course of chemotherapy, since this grade of toxicity was the main selection criterion of the study. The intensity of nausea and

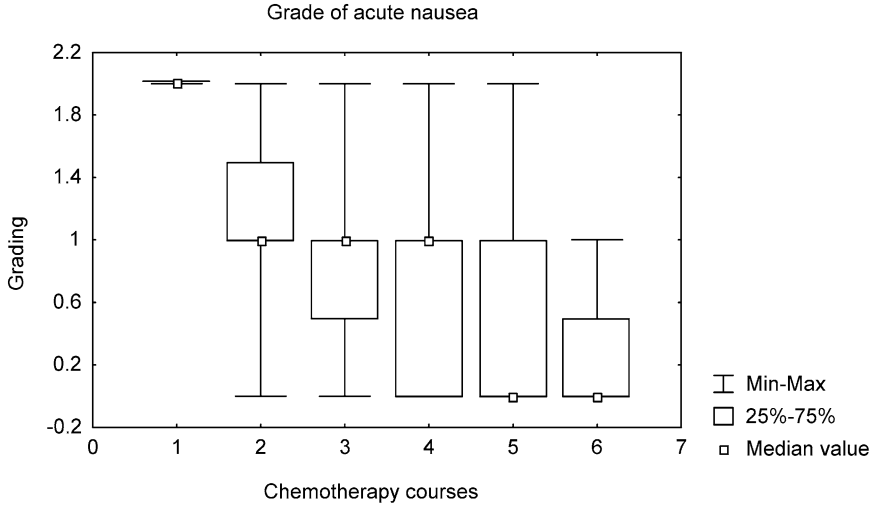

Fig. 1 Median grade (NCI-CTC) of acute nausea

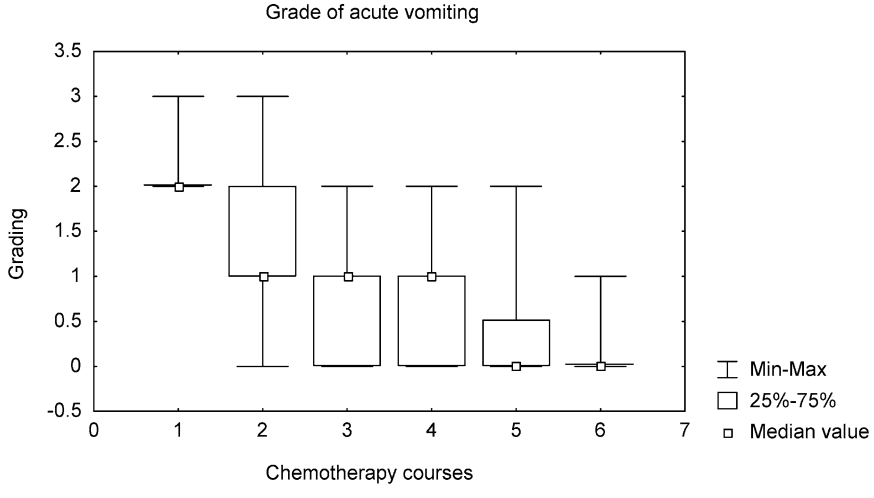

Fig. 2 Median grade (NCI-CTC) of acute vomiting

Table 1 Nauseaand vomiting intensities (median values) after chemotherapy according to NCI-CTCgrade and VAS score

	Course of chemotherapy					
	1	2	3	4	5	6
No. of patients[a]	26	26	26	22	11	7
Acute nausea grade	2	1	1	1	0	0
Acute nausea VAS score	10	5	3.5	3	2	0
Acute vomiting grade	2	1	1	1	0	0
Delayed nausea grade	2	1	1	0	0	0
Delayed vomiting grade	1	1	0	0	0	1

[a]Some patients (maximum one per course) lackedone or more toxicity measurements

vomiting progressively diminished from the first to the subsequent courses of chemotherapy.

The greatest reduction of these symptoms was recorded between the first and the second courses (Figs. 1 and 2). The differences in acute nausea (both measured in terms of NCI-CTC grade and VAS score) and in acute vomiting (measured by NCI-CTC grade) between the first and second courses were highly significant (Wilcoxon's matched pairs test; Table 1): the median grade of acute nausea was 2 during the first course and 1 during the second course (P =0.0001; Fig. 1); the median VAS score of acute nausea was 10 during the first course and 5 during the second course (P =0.0002) (data not reported); the median grade of acute vomiting was 2 during the first course and 1 during the second course (P =0.0003; Fig. 2). The average relative reduction in acute nausea and acute vomiting grade from the first to the second course was 48% (95% CI 34–62%) and 48% (95% CI 31–65%), respectively. Among the 26 patients enrolled, 19 (73%) showed a reduction in nausea and vomiting of at least one grade after their first exposure to midazolam (Table 2). Among the remaining 7 patients who did not experience any benefit with midazolam, 5 had previously received benzodiazepines chronically.

Six patients (23%) had no acute emesis during the second course, and were defined as complete responders (Table 2). The percentage of patients experiencing no acute vomiting during the first course (0%) was significantly different from that in the second course (23%) (P =0.02, Fisher's exact test). The intensities of acute nausea and vomiting differed significantly between the group of complete responders and the remaining patients from the second course through the fourth course (P <0.05, Mann-Whitney U -test). Patients showing a complete response during the second course had no acute emesis even during subsequent courses (one received three courses, four received four courses and one received five courses), with the exception of one patient who experienced grade 1 acute vomiting during the fourth course without acute vomiting during the fifth course. During the third course, five further patients, who had experienced grade 1–3 acute vomiting during the previous course, had no acute emesis, for a total of 11 patients showing complete absence of emesis. Nine of these patients received a fourth course, four also received a fifth course and two a sixth course, and none of them experienced acute emesis, apart from the patient who had grade 1 acute vomiting during the fourth course.

Nonparametric analysis of variance showed a significant difference in acute nausea, measured in terms of both NCI-CTC grade and VAS score, and acute vomiting among all the six courses of chemotherapy administered (Friedman ANOVA, P <0.0001 for acute nausea grade, acute nausea VAS score and acute vomiting grade). ANOVA retained its significance for all these variables after exclusion of the first course of therapy, and the intensity of symptoms decreased as the number of the courses administered in-

Table 2 Intensity of symptoms from course 1 through course 6 presented as the number of patients with each grade of each toxicity.Some patients (maximum one per course) lacked one or more toxicity measurements

	Course of chemotherapy											
	1 (n =26)				2 (n =26)				3 (n =26)			
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3
Acute nausea	0	0	26	0	5	14	7	0	7	15	4	0
Acute vomiting	0	0	20	6	6	12	6	2	11	11	4	0
Delayed nausea	4	8	13	0	6	9	10	0	7	14	4	0
Delayed vomiting	10	4	11	0	9	9	7	0	14	7	4	0
	Course of chemotherapy											
	4 (n =22)				5 (n =11)				6 (n =7)			
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3
Acute nausea	7	12	2	0	7	2	2	0	5	2	0	0
Acute vomiting	9	12	1	0	8	1	2	0	6	1	0	0
Delayed nausea	11	6	4	0	7	3	1	0	6	1	0	0
Delayed vomiting	13	3	5	0	7	2	2	0	3	4	0	0

creased. However, the *P* values were always lower when all six courses were included in the analysis, rather than when only the second through the sixth course were included. Furthermore, comparing each course with any subsequent course, significant differences in acute nausea, measured in terms of either the VAS scale or NCI-CTC grade, and in acute vomiting were observed only between the first and second, the first and third, and the first and fourth course (after Bonferroni correction for multiple comparisons).

Discussion

The principal aim of antiemetic treatment is the complete prevention of nausea and vomiting [13]. The combination of a 5-hydroxytryptamine 3 receptor antagonist with a corticosteroid is the recommended standard therapy for prevention of acute emesis caused by a highly emetogenic chemotherapy [13]. Anecdotal reports suggest that sedating a patient may be of value in cases of refractory emesis [14]. Thus, the use of various neuroleptic agents or tranquillizers, such as benzodiazepines, is suggested in the ASCO guidelines [13].

The primary goal of this study was to determine whether midazolam was able to effectively protect patients with acute nausea and vomiting resistant to the recommended standard antiemetic therapy. To our knowledge this is the first study in which midazolam has been evaluated in this challenging clinical scenario. Our data seem to suggest that midazolam was effective and well tolerated. The intensity of both nausea and vomiting progressively diminished from the first to subsequent courses of chemotherapy and the greatest reduction of toxicity was recorded between the first and second courses. These differences, measured in terms of NCI-CTC grade or VAS score, were highly significant. Nevertheless our data should be viewed with caution. We are aware that only 11 and 7 patients were evaluated during the fifth and sixth courses. In addition, our results could reflect a bias due to the selection of patients with worse symptoms, considering the criteria of enrollment into the study. It is noteworthy that all treatments were performed in the outpatient setting and, owing to the short half-life of midazolam, the patients were able to go home without assistance. The cost of one cycle of treatment was €4. Thus midazolam showed a low economic burden in managing refractory acute emesis. Among 26 patients, 19 (73%) benefited by midazolam (Table 2). Of the remaining 7 nonresponding patients, 5 had previously received benzodiazepines.

Refractory emesis after chemotherapy continues to represent a crucial clinical challenge [13]. Recently, aprepitant has been shown to provide consistently superior protection against chemotherapy-induced nausea and vomiting compared with standard therapy in patients receiving highly emetogenic cisplatin-based chemotherapy. These results represent an important medical advance that can importantly enhance the supportive care of cancer patients. Nevertheless, our data seem to suggest that midazolam may be a useful adjunct to standard antiemetic drugs. Since our study was open-label without a placebo control, the results should be regarded as preliminary. Further prospective randomized studies are needed before drawing any firm conclusions.

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