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An effective five-drug antiemetic combination for prevention of chemotherapy-related nausea and vomiting

Experience in eighty-four patients*

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Summary. Antiemetics of known efficacy have been shown to block mainly one of three neurotransmitter receptors in the brain. A combination of antiemetics, designed specifically for outpatient use and consisting of metoclopramide, thiethylperazine, diphenhydramine, dexamethasone, and diazepam, is capable of blocking multiple sites in the emesis pathway. Eighty-four patients receiving highly emetic chemotherapy (85% received cisplatin) completed 200 trials of this five-drug combination using two similar regimens. Complete control (i.e., no nausea or vomiting) was achieved in 45% and two or fewer episodes of vomiting was experienced in 72% of these 200 trials. The mean number of vomiting episodes was 1.65, the median 1.0, and the range 0–15. Sedation was nearly universal, although no serious toxicity was encountered. Thus, this antiemetic combination designed for outpatient use proved highly effective in controlling nausea and vomiting associated with highly emetic anticancer treatment.

Introduction

Nausea and vomiting induced by anticancer drugs continues to be a significant problem in the management of cancer patients. Not only are these side effects unpleasant, but they can also lead to a number of medical complications and to the abandonment of potentially curative therapy. Several recent reviews have discussed the need for a simple, effective outpatient antiemetic regimen capable of preventing this dreaded problem [1, 5, 19].

Lack of success with standard antiemetic drugs when used with the more emetic chemotherapeutic regimens has led to the evaluation of a number of newer agents. In recently published studies, both metoclopramide and dexamethasone have shown efficacy when administered in high doses [2, 4, 7, 20]. We recently reported comparable antiemetic efficacy for these two drugs when administered orally with no evidence of overlapping toxicities [3].

Antiemetics have been shown to block mainly one of three neurotransmitter receptors in the brain [13]. Combining antiemetic drugs with differing mechanisms of action and toxicities could potentially improve control of chemotherapy-induced nausea and vomiting. This hypothesis has been supported by clinical experience in hospitalized patients [9, 14].

Based upon our success with a five-drug parenteral combination in treating intractable nausea and vomiting induced by cisplatin [14], we have combined these same drugs into an oral and parenteral regimen suitable for use in outpatients. Our experience with this five-drug combination in 84 outpatients forms the basis of this report.

Materials and methods

All patients had histologically proven malignancy and were receiving chemotherapy at the University of Arizona Cancer Center. Patients being treated with actinomycin D, cis-platinum, dacarbazine (DTIC), or nitrogen mustard as part of their chemotherapy were eligible. Those patients receiving less potentially emetic regimens were excluded from this study unless they had failed prior antiemetics. Also excluded were patients less than 16 years of age, insulin-dependent diabetics, patients with known psychoses, and those whose respiratory status would not allow sedative treatments. Informed consent was obtained in all cases after the treatment regimen had been fully explained.

Table 1. Five-drug antiemetic regimen A

		At bedtime[a]	Every 4 h × 5[b]
Oral			
Dexamethasone	12 mg	×	×
Diazepam	5 mg	×	×
Thiethylperazine	10 mg[c]	×	×
		Before chemotherapy[d] −30 min	After chemotherapy[d] +30 min
Parenteral (IV)			
Dexamethasone	20 mg	×	×
Diphenhydramine	25 mg	×	×
Metoclopramide	1 mg/kg	×	×

[a] Night prior to chemotherapy
[b] On day of chemotherapy
[c] Thiethylperazine continued as necessary
[d] IV chemotherapy given over a 1 h period

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Table 2. Five-drug antiemetic regimen B

		Before chemotherapy[a] −30 min	After chemotherapy[a] +30 min	Day of chemotherapy Every 4 h × 4
Oral				
Dexamethasone	12 mg			×
Diazepam	5 mg	×	×	×
Thiethylperazine[b]	10 mg	×	×	×
Parenteral (IV)				
Dexamethasone	20 mg	×	×	
Diphenhydramine	25 mg	×	×	
Metoclopramide	1 mg/kg	×	×	

[a] Chemotherapy given over a 1 h period
[b] Thiethylperazine continued as necessary

The five drugs were dexamethasone, metoclopramide, diphenhydramine, diazepam, and thiethylperazine. In the first 45 patients, the antiemetics were started the night prior to anticancer therapy (regimen A). However, because the nighttime dosing required a delay in initiating chemotherapy, we subsequently treated a second group of 39 patients with a similar regimen, which started all antiemetic treatment 30 min before chemotherapy (regimen B). Details of these two regimens (A and B) are shown in Tables 1 and 2. In both regimens, thiethylperazine was continued orally the following day if needed. No specific dietary recommendations were made.

Assessment was by nurse monitoring and by standard questionnaire completed by clinic personnel and participating patients on the day of treatment and the following day. Telephone contact was used to improve the validity of questionnaires. Specific inquiry was made regarding patient compliance and anticipated toxicities of antiemetic therapy, including sedation, dystonic reactions, and frequency of bowel movements. Also recorded were nausea duration in hours, nausea severity on a five-point scale, and the number of vomiting episodes. Responses were recorded using the criteria in Table 3. Comparisons were analyzed by chi-square two by two tables.

Table 3. Evaluation criteria for nausea and vomiting control[a]

	Nausea		Vomiting
Control	Duration	Severity[b]	Number Episodes
Excellent	0 h	0	0
Good	<6 h	1–2	1–2
Fair	>6 h	3	3–5
Poor	>6 h	4–5	>5

[a] Numbers reflect the maximum allowable within each category: for example, mild (grade one) nausea of less than 6 h duration but with three episodes of emesis would be classified in the fair category
[b] Severity graded individually by patients on a five-point scale (1 = mild, 5 = severe)

Table 4. Results. Patient characteristics

	Regimen A	Regimen B
Number of patients	45	39
Number of trials	115	85
Female/male	38/7	31/8
Age: Mean	49	53
Range	17–76	18–80
Prior antiemetic	35	13
Cisplatin combination	39 (87%)	32 (82%)
Mean dose/patient	96 mg	87 mg
Range	54–225 mg	50–190 mg

Results

Eighty-four patients completed 200 antiemetic trials. Forty-five patients received 115 courses of regimen A, and 39 patients completed 85 trials of regimen B. Three patients did not complete the treatment or evaluation forms and were excluded from the study. One patient admitted to not taking the oral medications after leaving the clinic and the second was lost to follow-up prior to completion of the study questionnaire. The third patient had received substantial prior chemotherapy and asked to be withdrawn from the study after vomiting three times. She subsequently received the five-drug IV regimen [14] without additional vomiting.

The average age of the patients was 51 years (range 17–80), and the median was 53 years. Sixty-nine patients were female. The tumor types represented included gynecologic cancer (cervical 23, ovarian 19, endometrial 4, uterine sarcoma 3, choriocarcinoma 2, fallopian tube cancer 1); non-small-cell lung cancer 7; Hodgkin's disease 7; breast cancer 3; non-Hodgkin lymphoma 3; two each of soft tissue sarcoma, head and neck, and urinary bladder cancer; and one each of prostate, rectal, urethral and gallbladder cancer. Forty-eight patients had received antiemetics with prior antineoplastic treatments, including 4 who had previously received regimen A before enrolling to receive regimen B. Eighty-five percent of patients received cisplatin-based combination chemotherapy while the remainder received various other combinations, which included nitrogen mustard, doxorubicin, or dacarbazine. One patient had previously experienced nausea and vomiting with administration of bisantrene and was thus eligible. Cisplatin was given with saline hydration and mannitol in an intravenous infusion over 1 h. For the majority of patients, the dose of cisplatin was 50–60 mg/M^2 (range 40–100 mg/M^2). Patient characteristics by regimen are listed in Table 4.

On the day of chemotherapy, overall control (good-to-excellent response) was achieved in 65% of trials with no difference between regimens ($P=0.42$). Total control of nausea and vomiting was obtained in 45% of the 200 treatments and was more commonly found with regimen B (56%) than with regimen A (37%) ($P=0.007$). Results of all courses of antiemetic therapy are shown in Table 5.

When the first five-drug antiemetic combination experience for each patient is analyzed, similar results are found with good-to-excellent control achieved in 68% of patients. Details or response are listed in Table 6. For the entire group, the mean number of vomiting episodes was 1.65, the median 1.0, and the range 0–15 episodes.

Control of nausea and vomiting also continued to the day after chemotherapy with complete control achieved in 158 trials (79%) and good control in 26 (13%). The efficacy of these regimens was sustained through repeated courses of chemotherapy.

Seven of the 84 patients received 16 courses of high-dose cisplatin (100 mg/M^2) in combination with 1–2 other anticancer drugs. These patients experienced antiemetic protection similar to that of the entire group of patients, with 50% having excellent and 19% good control ($P=0.67$).

The 48 patients with prior antiemetic experience had received single antiemetics as well as various combinations. Included among these 48 patients were 18 who had been enrolled in a previous evaluation of dexamethasone versus placebo. Responses were uniformly poor to both dexamethasone and to placebo. All 18 patients were then successfully rescued with a parenteral five-drug regimen similar to the regimens evaluated in this report [14]. The remaining 30 individuals generally reported poor results with their respective previous antiemetics. In the current study, protection tended to be less complete in these previously treated patients, with 67% good and excellent results but with only 38% excellent protection. Conversely, in those patients who had never received prior chemotherapy or antiemetics, excellent protection was achieved in 58%.

In keeping with the metoclopramide experience recently reported by Meyer et al. [19], we observed improved nausea and vomiting control in older patients (Table 7). In patients over the age of 60, excellent control of emesis was achieved in 57%, and less than three episodes of vomiting were observed in 80% of patient trials. In contrast only 37% of patients under 60 had no emesis, and fewer than three episodes of vomiting were observed in 59% of patient trials ($P<0.005$).

The most frequently encountered side effect was sedation, although all patients remained ambulatory with assistance and could be safely discharged from the clinic. Only 5 patients were free of sedative effects. Thirty-five individuals (41%) reported nervousness, and 18 (21%) noted looseness of stool. Despite receiving two 25-mg doses of diphenhydramine, suspected dystonic reactions occurred one time in each of four patients (5% of patients, 2% of treatment courses) aged 22, 35, 52, and 55 years. These reactions were either transient or responded to additional diphenhydramine. Other reported side effects included blurred vision, dysuria, depression, headache, itching, singultus, fatigue, diphoresis, and fever. No serious toxicity was encountered with either five-drug regimen.

Table 5. Results of all courses of the five-drug regimen (initial and subsequent)

		Regimen A (115)	Regimen B (85)	Combined (200)
Vomiting episodes				
0	%	46	62	53
1–2	%	23	15	19
>2	%	31	23	28
Mean number		1.76	1.54	1.65
Median number		1.0	1.0	1.0
Range		0–10	0–15	0–15
Nausea and vomiting				
Control[a]				
Excellent	%	37	56	45
Good	%	28	15	23

[a] See criteria **Table 3**

Table 6. Results of the initial patient experience with each five-drug regimen

		Regimen A (45)	Regimen B (39)	Combined (84)
Vomiting episodes				
0	%	40	66	52
1–2	%	29	8	19
>2	%	31	26	29
Mean number		1.73	1.64	1.68
Median number		1.0	1.0	1.0
Range		0–10	0–15	0–15
Nausea and vomiting				
Control[a]				
Excellent	%	38	64	50
Good	%	28	6	18

[a] See criteria **Table 3**

Table 7. Effects of age vs emesis control. Total trials, combined Regimens A and B

Age	≥60	<60	Total
Nausea and vomiting			
Control[a]			
● Excellent	45 (57%)	45 (37%)	90 (45%)
● Good	18 (23%)	27 (22%)	45 (23%)
● Fair	7 (9%)	25 (21%)	32 (15.5%)
● Poor	9 (11%)	24 (20%)	33 (16.5%)
Total	79	121	200 (100%)

[a] See criteria **Table 3**
Excellent ≥60 vs <60 $P = 0.005$
Excellent + Good ≥60 vs <60 $P = 0.003$

Discussion

Although there have been recent advances in single-agent antiemetic treatment, chemotherapy-induced nausea and vomiting remains a major obstacle in patient acceptance of anticancer therapy. It has been estimated that up to 50% of patients will refuse or delay potentially curative therapy because of severe nausea and vomiting [10].

Even today little information exists regarding the fundamental mechanisms by which anti-cancer drugs cause

nausea and vomiting. As might be suspected from experiments with noxious agents such as apomorphine, the chemoreceptor trigger zone is probably involved. Additionally, the cerebral cortex and afferent gastric impulses may stimulate the vomiting center resulting in emesis. Recently, Peroutka and Snyder have demonstrated that effective antiemetic drugs may block at least one neuroreceptor type (histaminic, muscarinic cholinergic, or dopaminergic) in the central nervous system [13]. Of note was their demonstration that no single agent blocked all three receptors with comparable potency. Antiemetics of differing mechanism of action and toxicities could protentially improve protection from nausea and vomiting if given in combination. We have previously reported that a parenteral five-drug combination capable of blocking multiple neurotransmitter receptors resulted in almost complete emesis control when given to patients with intractable, cisplatin-induced vomiting [14]. A similar combination has been successfully applied to inpatients by others [9].

We have now reported our experience with a five-drug oral and parenteral combination that can easily be used in outpatients. These five drugs combine a number of antiemetic mechanisms without overlapping toxicites. Metoclopramide and thiethylperazine are potent dopamine antagonists and effective antiemetics and, compared with other phenothiazines, thiethylperazine is less sedating [12]. Metoclopramide also acts as a stimulant on the gut and prevents the gastric atony associated with nausea [18]. High-dosage metoclopramide is effective against cisplatin-induced emesis [7, 20], while low-dosage regimens are only marginally active [6, 8]. Diphenhydramine combines antihistaminic antiemetic activity [13] with a potential for preventing extrapyramidal effects induced by thiethylperazine or metoclopramide. Diazepam has demonstrated antiemetic activity as well as desirable anxiolytic and amnestic properties [17].

High-dosage dexamethasone and methylprednisolone, have shown favorable results in a number of antiemetic trials without significant toxicity from short-term use [2, 4, 16]. The mechanism of action of these agents remains unclear, although an anti-prostaglandin effect has been suggested [16]. An optimal dose of dexamethasone for control of emesis in most patients has been suggested to be in the range of about 40 mg given over a 12-h period, beginning prior to chemotherapy. However, about 20% will benefit from higher doses [4].

Both regimens A and B employed the same five drugs; however, the oral schedule in regimen A began the night before chemotherapy while, in regimen B, all antiemetic drugs were started 30 min before anticancer therapy. Based on our results, it appears unnecessary to initiate antiemetic coverage more than 30 min prior to chemotherapy. Control of emesis tended to be more complete with regimen B. This trend is most likely explained by the increased percentage of patients with previous, usually unsuccessful, antiemetic experience in the regimen A group. Alternatively, the longer interval between initiation of antiemetic treatment and chemotherapy may have resulted in increased anticipatory nausea and vomiting with the first regimen.

The significant difference in the nausea and vomiting control achieved in patients above and below the age of 60 is of considerable interest. Similar observations reported by Meyer could not be explained by differences in serum metoclopramide levels [11]. Likewise, increased sensitivity to diazepam has been reported for elderly patients despite the presence of lower serum concentrations when compared to younger patients [15]. As suggested by Meyer, these differences may best be explained by increased central nervous system sensitivity to antiemetics rather than by differences in drug protein binding or reduced potential for emesis in older patients.

We believe that a multidrug combination capable of blocking the emesis response at multiple sites offers broad clinical applicability and an important new direction in the prevention and treatment of chemotherapy-induced vomiting. Advantages include ease of outpatient administration and lower cost ($ 61 vs $ 101–$ 168 U.S. dollars) compared with reported high-dosage metoclopramide regimens. In addition, toxicity can be minimized with combination regimens by avoiding increasing drug doses and overlapping toxicities. Based on our successful experience with this five-drug combination, further research is indicated to develop even more effective combination regimens for the control of nausea and vomiting in cisplatin-treated patients.

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