The Antiemetic Efficacy of Secobarbital and Chlorpromazine Compared to Metoclopramide, Diphenhydramine, and Dexamethasone

A Randomized Trial

PAUL D. RICHARDS, MD,* MORRIS A. FLAUM, MD, MARILYN BATEMAN, RN, AND CARL G. KARDINAL, MD

The efficacy of secobarbital sodium plus chlorpromazine (SC) in the prevention of cisplatin induced emesis was compared to the combination of metoclopramide, diphenhydramine, and dexamethasone (MDD). Twenty-three patients were entered onto protocol. Eighteen were evaluable. Good to excellent antiemetic prophylaxis was obtained in 72% with MDD *versus* 17% with SC ($P < 0.01$). Sedation and anticholinergic side effects were more common with SC. Extrapyramidal reactions were more commonly seen with MDD. Significantly more patients preferred the combination of metoclopramide, diphenhydramine, and dexamethasone ($P < 0.05$).

Cancer 58:959–962, 1986.

THE INTRODUCTION of cisplatin into the chemotherapeutic armamentarium gave impetus to therapeutic attempts to control the associated severe nausea and vomiting. High-dose metoclopramide was the first truly effective antiemetic regimen for cisplatin.[1] This regimen has been subsequently improved[2] by the addition of diphenhydramine to prevent extrapyramidal side effects, and dexamethasone to increase the antiemetic efficacy and decrease the frequency of diarrhea. Yet metoclopramide is not a perfect antiemetic because of extrapyramidal side effects[3,4] and the high cost.[5]

Sevin *et al.*[6] demonstrated the antiemetic activity of the barbiturate–phenothiazine combination of pentobarbital sodium plus prochlorperazine with dexamethasone in patients treated with cisplatin regimens. They observed no vomiting in 22/30 (73%) patients. We postulated that barbiturates might enhance the antiemetic effect of phenothiazines through their sedative potential.

This study was undertaken to investigate the antiemetic efficacy of the relatively inexpensive regimen of secobarbital sodium and chlorpromazine (SC) compared to a metoclopramide, diphenhydramine, and dexamethasone regimen (MDD)[2] in a randomized cross-over trial.

From the Department of Internal Medicine, Section on Hematology and Oncology, Ochsner Clinic and Alton Ochsner Medical Foundation, New Orleans, Louisiana.

* Current address: Lewis-Gale Clinic, 1802 Braeburn Drive, Salem, VA 24153.

Address for reprints to Morris A. Flaum, MD, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, LA 70121.

The authors thank Don Samples, MD, and Archie Brown, MD, for allowing their patients to be placed on protocol and to Kirsten Sungaard-Riise, BS, for performing statistical analysis.

Accepted for publication November 15, 1985.

Materials and Methods

Patients were eligible for study if they required cisplatin chemotherapy for a malignant disease. No patients had prior cisplatin exposure or prior antiemetic treatment with metoclopramide, chlorpromazine, or secobarbital. Patients with severe chronic obstructive pulmonary disease (COPD), cirrhosis or hepatic failure, unstable angina or severe coronary artery disease, arrhythmias, diabetes mellitus, or acute intermittent or variegate porphyria were excluded. To be eligible for study, a Karnofsky performance status of 60% or greater was required, although one patient was allowed to enter with a Karnofsky score of 40% whose poor performance status was due to myelomatous involvement of the lumbar spine without other medical problems.

A later modification secondary to a possible treatment related death with SC excluded any patient with a history or clinical evidence of COPD, extensive (>50%) replacement of the liver by tumor, or age ≥70 years. Informed consent was obtained from all patients.

No other antiemetics, narcotics, or sedatives were administered within 24 hours of cisplatin therapy. All patients were hospitalized for intravenous (IV) hydration and mannitol diuresis. Input and output, blood pressure and pulse were monitored hourly for 8 hours after pre-

TABLE 1. Characteristics of 18 Evaluable Patients

Patient characteristics	
Age (yr)	
Range	26–67
Mean	52
Sex	
Male	6
Female	12
Karnofsky status (%)	
Range	40–100
Mean	79
Tumor types (no.)	
Ovarian and gynecologic	9
Head and neck	4
Lung	2
Other	3
Chemotherapy	
Cisplatin dose (mg/M^2)	
50–99	16
≥100	2
First antiemetic regimen	
SC	10
MDD	8

SC: secobarbital sodium + chlorpromazine; MDD: metoctopramide, diphenhydramine, and dexamethasone.

medication was begun. Cisplatin was administered by standard IV infusion over 60 minutes.

Patient Characteristics

Between January 1984 and November 1984, 23 patients were entered on protocol. Eighteen patients (Table 1) were evaluable having completed two cycles of cisplatin-based chemotherapy and having crossed over to the alternate antiemetic regimen, and will be considered in this report. This was the first exposure to cisplatin for all patients and to chemotherapy for 15 patients. The creatinine clearance prior to each course of therapy ranged from 53 to 206 ml/min (mean, 92 ml/min). The dose of cisplatin remained constant between cycle 1 and 2 for all patients. Ten patients received SC as their first antiemetic regimen and eight patients received MDD as their first antiemetic regimen. Of the five unevaluable patients, three died prior to a second cycle of cisplatin. Two deaths were unrelated to treatment, while one patient with COPD and extensive (90%) replacement of the liver with metastatic disease (unknown prior to autopsy) developed fatal congestive heart failure which may have been complicated by respiratory depression secondary to secobarbital plus chlorpromazine. Two patients did not receive the alternate antiemetic regimen. One preferred to remain on SC. The other remained on MDD due to temporary suspension of the protocol.

TABLE 2. Drug Dose and Schedule

Body surface area (M^2)	First dose (mg)		Second dose (mg)		Third dose (mg)
	S	C	S	C	C
1.25–1.49	125	25.0	100	25.0	25.0
1.50–1.74	150	37.5	125	37.5	37.5
1.75–1.99	175	50.0	150	50.0	50.0
≥2.00	200	62.5	175	62.5	62.5

Secobarbital and chlorpromazine doses were given intramuscularly 30 minutes before cisplatin and then repeated every 4 hours for one or two more doses, respectively.

S: secobarbital; C: chlorpromazine.

Study Design

Patients were alternately assigned to receive secobarbital plus chlorpromazine (SC) or metoclopramide, diphenhydramine plus dexamethasone (MDD) for the first cycle of cisplatin-containing chemotherapy and then were crossed over to the other antiemetic arm for the second cycle of chemotherapy. The patient then elected the optimal antiemetic regimen. The study was open label since the two regimens were delivered by different techniques, intramuscular (IM) *versus* IV, respectively.

Evaluation Techniques

A diary was provided for use by the patients, family members or friends, and the nurse for recording time of onset and duration of nausea and vomiting, as well as the number of emetic episodes and volume of emesis. Questionnaires were completed by nurses regarding observed side effects. The patient received a questionnaire regarding side effects and antiemetic preference the morning after chemotherapy treatment.

The patients were asked to assess the degree of sedation associated with the treatment according to the following scale: 1—none; 2—slept less than 3 hours; 3—slept at least 3 hours, but not more than 6 hours; 4—slept 6 hours or more.

Drug Dose and Schedule

Secobarbital was given IM 30 minutes prior to cisplatin and then repeated once, at a dose reduced by 25 mg, in 4 hours. Secobarbital doses adjusted for body surface area (BSA) were as listed in Table 2. Secobarbital and chlorpromazine dose modifications were made after a possible treatment-associated death. Patients with BSA ≥1.75 M^2 received secobarbital 150 mg IM for both injections and chlorpromazine at 50 mg IM for all three injections.

The metoclopramide, diphenhydramine, dexamethasone regimen was utilized as described by Tyson *et al.*[2] Metoclopramide (2 mg/kg) IV was given 30 minutes prior to cisplatin and then every 2 hours for 3 doses. Diphenhydramine 50 mg IV and dexamethasone 20 mg IV were given with the first dose of metoclopramide.

Data Analysis

Patients were considered evaluable if they completed two cycles of cisplatin-based chemotherapy and had received both antiemetic regimens.

Analysis of variance with repeated measures was used to compare the relative efficacy of SC *versus* MDD for number of emetic episodes, duration of nausea and vomiting, and emesis volume.

McNemar's test for change was used to evaluate the patient's antiemetic preference and regimen efficacy.[7] Side effects of the two regimens, including sedation, diarrhea, extrapyramidal, central nervous system, cardiovascular, and anticholinergic side effects, were compared by the McNemar's test for change.

Linear regression analysis was used to calculate the correlation coefficient between the number of vomiting episodes and the degree of sedation with either SC or MDD.

Results

Efficacy

The efficacy and toxicity of the two different regimens are compared in Table 3. The average number of emetic episodes for MDD was 2.89, significantly less than the 7.83 episodes noted with SC. Complete or major antiemetic prophylaxis (0, 1, 2 emetic episodes)[2] was experienced by 72% of patients in the MDD treatment arm compared to 17% in the SC treatment arm. The median number of emetic episodes was 1 in the MDD regimen and 5.5 in the SC regimen. Seven patients had complete antiemetic prophylaxis with MDD; only one of these patients had no emesis with SC. The three patients with complete or major emetic prophylaxis with SC had similar responses to MDD.

The mean duration of nausea and vomiting was less with MDD (2.03 hours) than with SC (4.27 hours). The volume of emesis for each regimen did not vary significantly. Most importantly, patients preferred the MDD regimen over SC 12:3, with 3 having no preference. Eleven of the 12 preferring MDD did so on the basis of better emetic control. Only 1 of the 3 patients preferring the SC regimen did so on the basis of adverse effects of MDD.

TABLE 3. Results of Treatment With MDD and SC

Parameter	MDD	SC	*P* value
Efficacy			
Mean no. of emetic episodes	2.89	7.83	$P < 0.01$
Median no. of emetic episodes	1	5.5	
No. with complete or major antiemetic results (2 or less episodes of emesis)	13	3	$P < 0.01$
Mean duration of nausea, vomiting (h)	2.03	4.27	$P < 0.01$
Average emesis volume (cc)	206	399	P = NS
Patient's preference (no preference = 3)	12	3	$P < 0.05$
Toxicity			
Sedation (severe = slept 3 h)	6	13	$P < 0.02$
Extrapyramidal	8	2	$P < 0.02$
Akathisia	6	1	
Facial spasm or trismus	5	1	
Body spasms	5	2	
CNS	10	9	P = NS
Anxiety	7	1	
Insomnia	7	3	
Euphoria	1	2	
Hangover	0	6	
Anticholinergic	6	12	P = NS
Dry eyes or mouth	4	12	
Blurred vision	1	3	
Urinary hesitancy	0	2	

MDD: metoclopramide, diphenhydramine, and dexamethasone; SC: secobarbital + chlorpromazine; CNS: central nervous system; NS: not significant.

Toxicity

Sedation was severe (causing ≥3 hours sleep) in more SC patients (72%) than in the MDD patients (33%). Anticholinergic side effects of dry eyes or mouth, blurred vision, and urinary hesitancy were more common with SC (67%) than with MDD (33%). Treatment-associated diarrhea was noted in five patients on MDD therapy and in ten patients on SC therapy. Extrapyramidal side effects, akathisia, or muscular spasms were more frequently associated with the MDD treatment in contrast to the SC treatment (11%).

Although central nervous system (CNS) side effects were numerically similar in both treatment groups, the type of CNS toxicity differed. MDD was attendant with more anxiety, while SC was uniquely associated with a hangover. Two episodes each of urinary incontinence (due to sedation) and injection site pain were exclusively noted with SC.

There were no serious cardiovascular or respiratory side effects, except for one patient with fatal congestive heart failure who may also have had respiratory depression while receiving the SC treatment. Mild sinus tachycardia (<140 beats per minute) occurred occasionally. Although a number of patients in both groups reported lightheadedness, there was no hypotension.

Discussion

Nausea and vomiting are severe and debilitating complications of cancer chemotherapy. The phenothiazines have, until recently, been the mainstay of antiemetic therapy.[8] Attempts at more effective antiemesis have utilized a number of single agents including metoclopramide,[1] haloperidol,[9,10] droperidol,[11] lorazepam,[12] tetrahydrocannabinol,[13] and corticosteroids.[14] Combinations of active

antiemetics are now being studied to effect control of the most emetogenic chemotherapeutic agents.

Kris *et al.* demonstrated improved control of cisplatin-induced emesis with combinations of metoclopramide, dexamethasone, and diphenhydramine with a decrease in the incidence of side effects.[15] Combinations of barbiturates and phenothiazines have long been thought to result in effective antiemesis. Therefore, we evaluated the antiemetic efficacy of secobarbital and chlorpromazine and compared these to a metoclopramide, diphenhydramine, and dexamethasone regimen.

This study has demonstrated the superiority of the latter regimen for the control of cisplatin-induced emesis. Sedation and anticholinergic toxicity were greater with SC. The MDD regimen, however, commonly produced extrapyramidal side effects (44% of patients).

Although sedation is a common side effect of various antiemetic therapies, this side effect is discordant with the antiemetic activity of the therapy. There was no significant correlation between the number of emetic episodes and extent of sedation with either SC ($r = 0.282$, $P > 0.10$) or MDD ($r = 0.141$, $P > 0.10$). Indeed, the SC regimen produced more sedation than the MDD regimen, but with inferior emetic inhibition. The attendant sedation may result in enhanced toxicity and complications of therapy. Moertel and Reitemeier[16] found sodium pentobarbital exerted its expected sedative effect, but had no more antiemetic activity than placebo for 5-FU chemotherapy.

Our results differ from those of Krebs *et al.*[17] who found the combination of IV pentobarbital, prochlorperazine, and dexamethasone superior to single-agent metoclopramide in terms of antiemetic efficacy. Eighty-one percent of their patients treated with the combination regimen had less than three emetic episodes *versus* 17% of our patients treated with IM secobarbital plus chlorpromazine.

Similarly, Sevin *et al.*[6] noted beneficial effects with the combination of pentobarbital, dexamethasone and prochlorperazine in patients treated for cisplatin-induced emesis. They noted that 73% of their patients had no vomiting when the combination was used as primary therapy.

Several differences may account for these results, including the substitution of secobarbital for pentobarbital and chlorpromazine for prochlorpromazine in our series, nocturnal administration, and an IM *versus* an IV route of administration. The addition of dexamethasone to the pentobarbital–prochlorpromazine combination may also enhance the antiemetic effect, since Kris *et al.* have noted an improvement in emetic control when dexamethasone is added despite dosage reduction of metoclopramide.[15]

Our results demonstrate the inferiority of the combination of secobarbital and chlorpromazine when compared to high-dose metoclopramide, diphenhydramine, and dexamethasone for cisplatin-based chemotherapy. Further studies will be required to optimize the latter regimen and to identify other effective combinations.

REFERENCES

1. Gralla RJ, Itri LM, Pisko SE *et al.* Antiemetic efficacy of high-dose metoclopramide: Randomized trials with placebo and prochlorperazine in patients with chemotherapy induced nausea and vomiting. *N Engl J Med* 1981; 305:905–909.

2. Tyson LB, Gralla RJ, Clark RA, Kris MG. Combination antiemetic trials with metoclopramide. *Proc Am Soc Clin Oncol* 1983; 21:91.

3. Kris MG, Tyson LB, Gralla RJ. Extrapyramidal reactions with high-dose metoclopramide. *N Engl J Med* 1983; 309:433.

4. Graham-Pole J, Engel S. Dose-related extrapyramidal effect of metoclopramide in children receiving chemotherapy. *Proc Am Soc Clin Oncol* 1984; 3:104.

5. Nelson EA. Letter to the Editor. *N Engl J Med* 1982; 307:250.

6. Sevin BU, Martinez-Esteve I, Averette HE. Combination antiemetic medication in the management of cisplatin associated vomiting. *Proc Am Soc Clin Oncol* 1983; 2:97.

7. Armitage P. Statistical Methods in Medical Research. New York: John Wiley & Sons, 1971.

8. Stoudemire A, Cotanch P, Laszlo J. Recent advances in the pharmacologic and behavioral management of chemotherapy-induced emesis. *Arch Intern Med* 1984; 144:1029–1033.

9. Shields KL, Ballinger CM, Hathaway BN. Antiemetic effectiveness of haloperidol in human volunteers challenged with apomorphine. *Anesthiol Analg* 1971; 50:1017–1024.

10. Grunberg SM, Gala KV, Lampenfield M *et al.* Comparison of the antiemetic effects of high dose intravenous metoclopramide and high dose intravenous Haldol in a randomized double-blind crossover study. *Proc Am Soc Clin Oncol* 1983; 2:85.

11. Citron ML, Johnston-Early A, Boyer MW, Krasnow SH, Priebat DA, Cohen MH. Droperidol (DP): Optimal dose and time of initiation. *Proc Am Soc Clin Oncol* 1984; 3:106.

12. Maher J. Intravenous lorazepam to prevent nausea and vomiting associated with cancer chemotherapy. *Lancet* 1981; 1:91–92.

13. Sallan SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: A randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *N Engl J Med* 1980; 302: 135–138.

14. Markman M, Sheidler V, Ettinger DS, Quaskey SA, Mellits ED. Antiemetic efficacy of dexamethasone. *N Engl J Med* 1984; 311:549–552.

15. Kris MG, Gralla RJ, Tyson LB *et al.* Improved control of cisplatin-induced emesis with high-dose metoclopramide and with combinations of metoclopramide, dexmethasone, and diphenhydramine. *Cancer* 1985; 55:527–534.

16. Moertel CG, Reitemeier RJ. Controlled clinical studies of orally administered antiemetic drugs. *Gastroenterology* 1969; 57:262–268.

17. Krebs H-B, Myers MB, Wheelock JB, Goplerud DR. Combination antiemetic therapy in cisplatin-induced nausea and vomiting. *Cancer* 1985; 55:2645–2684.