Acta Oncologica Vol. 30 No. 3 1991

FROM HOSPITAL UNIVERSITARIO SAN CARLOS, AND UPJOHN MEDICAL DEPARTMENT, MADRID, HOSPITAL GERMANS TRIAS Y PUJOL, BADALONA, AND HOSPITAL GENERAL DE NAVARRA, PAMPLONA, SPAIN.

THE ANTIEMETIC EFFICACY OF THIETHYLPERAZINE AND METHYLPREDNISOLONE VERSUS THIETHYLPERAZINE AND PLACEBO IN BREAST CANCER PATIENTS TREATED WITH ADJUVANT CHEMOTHERAPY (FLUOROURACIL, DOXORUBICIN AND CYCLOPHOSPHAMIDE)

A randomized, double-blind, cross-over trial

E. DIAZ-RUBIO, M. MARTIN, R. ROSELL, J. J. VALERDI, J. L. GONZALEZ-LARRIBA and J. J. BARRIGA

Abstract

Forty-six women with breast cancer treated with adjuvant FAC (fluorouracil, doxorubicin and cyclophosphamide) entered a multicenter, randomized, double-blind, cross-over trial in which thiethylperazine (T) (6.5 mg p.o every 8 h × 3 days) plus methylprednisolone (MP) (250 mg i.v. × 2 doses) was compared with thiethylperazine plus placebo. Forty-four patients were evaluable for efficacy. T + MP was significantly better in reducing vomiting ($p < 0.01$) and nausea ($p < 0.02$). The complete protection rate against vomiting was 36% for T + MP compared to 18% for T + placebo, and the percentage of nausea grades 0 + 1 (none or slight) was 59% and 27% respectively. The patient preference after cross-over was strikingly in favor of T + MP (70% versus 13%) ($p < 0.001$). The most important side-effects of T + MP were facial flushing (22%) and euphoria (27%). Other side-effects, such as dryness of the mouth and sedation, were common after both treatments. In conclusion, the study suggested that T + MP is superior to T alone in protecting from nausea and vomiting induced by FAC.

Key words: Cancer chemotherapy, FAC (5-FU, doxorubicin, cyclophosphamide), nausea, vomiting, thiethylperazine, methylprednisolone, breast cancer.

Vomiting due to chemotherapy is one of the most common side-effects of anti-tumor treatment. It can, on occasion, be the cause of early interruption of potentially useful treatments. The FAC combination (fluorouracil, doxorubicin and cyclophosphamide) is frequently used in the treatment of breast cancer. Doxorubicin administered alone or in combination with other cytotoxic agents induces nausea and vomiting in up to 60% of the patients (1), and is considered a moderately (2) or severely (3) emetogenic agent.

In contrast to the vomiting induced by cisplatin, few trials have addressed the emesis caused by doxorubicin containing combination (4–9) and none specifically the emesis induced by FAC chemotherapy, in spite of the fact that this treatment induces vomiting and nausea in 97% of the cases (10). These trials have mainly evaluated the phenothiazines, which give complete or major protection in a minority of patients (4). The combination of phenothiazines with other antiemetic agents increases their protective activity, which, however, remains low. The combination of thiethylperazine and amitriptyline has thus been reported to prevent emesis in only 26% (5).

Corticosteroids have been shown to increase the antiemetic action of other agents both after cisplatin (11–13) and non-cisplatin containing (14–18) regimens. For doxorubicin containing regimens, however, only limited data are available.

We therefore started a multicenter, randomized, double-blind, cross-over trial in which the combination of a phenothiazine and methylprednisolone was compared with the same phenothiazine plus placebo.

Submitted 19 January 1990.
Accepted for publication 19 May 1990.

Material and Methods

Forty-six women with non-metastatic breast cancer in stages II A-B or III A-B, receiving adjuvant FAC (5-fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2, all i.v. on day 1, every 3 weeks) entered the trial. All patients were chemotherapy naïve, and they were treated as out-patients.

The patients were eligible if they had a Karnofsky index over 80 and no signs of diabetes, hypertension or peptic ulcer. Other criteria for exclusion were the presence of nausea and vomiting due to other causes, concomitant radiotherapy and use of narcotic analgesics or CNS sedatives.

After a written consent, the patients entered this randomized, double-blind, cross-over trial, in which each patient served as her own control. The randomization procedure and the coding of preparations were performed at the Upjohn Co., and the code remained unbroken until the study was completed. The trial was approved by the Spanish authorities and by the ethics committees of the participating hospitals. Patients in treatment arm A received thiethylperazine (T), 6.5 mg p.o. every 8 h during 3 days, and methylprednisolone (MP) 250 mg in 100 ml 0.9% NaCl solution half an hour before the start of chemotherapy and $1\frac{1}{2}$ h after it. Patients in treatment arm B received thiethylperazine at the same doses, plus placebo instead of the methylprednisolone, with the same administration. In the second cycle of chemotherapy, the patients received the alternative antiemetic treatment (cross-over). The trial was finished after evaluation of emesis following the second chemotherapy cycle.

The efficacy of the anti-emetic treatment was analysed by measuring the number of vomiting episodes and the intensity of nausea during the day of chemotherapy and the following four days. The patients documented each day on a diary card the number of emetic episodes and the intensity of nausea. Side-effects of the antiemetic treatment were also recorded on the same card. The grades used for vomiting were: complete protection (0 episodes), major protection (1–2 episodes), minor protection (3–5 episodes) and failure (more than 5 episodes). The intensity of nausea was assessed by a specially designed questionnaire which included the following scale: 0: no nausea 1: slight nausea, 2: moderate nausea and 3: severe nausea. Data on patient preference was obtained at the end of the second course. All data were collected and revised by the medical staff.

The χ^2-test for paired data was used for the statistical analysis.

Results

Of the 46 patients who entered the trial, 24 were allocated to arm A and 22 to arm B. Forty-four of these patients were fully evaluable. The two excluded patients (one in each arm) received no further FAC cycles (1 due to progression, 1 due to interruption of chemotherapy). In arm A 13/24 patients and in arm B 12/22 patients had an age >50 years.

Complete protection of vomiting was observed in 36% of the cases who received T + MP, and in 18% of those who received T + placebo ($p = 0.094$) (Table 1). Table 2 shows the percentage of complete protection during 1st and 2nd courses of chemotherapy for each group. The order of chemotherapy cycle had no significant influence on the prevention of vomiting.

Table 2

Complete protection (%) of vomiting during 1st and 2nd courses of chemotherapy for each group

Group A		Group B	
1st course (T + MP)	2nd course (T + placebo)	1st course (T + placebo)	2nd course (T + MP)
8/23 (34.7%)	5/23 (21.7%)	3/21 (14.2%)	8/21 (38%)

Table 1

Analysis of vomiting

	Thiethylperazine + methylprednisolone		Thiethylperazine + placebo
Complete protection (0 episodes)	16 (36.3%)	$p = 0.094$	8 (18.1%)
Major protection (1–2 episodes)	7 (15.9%)	$p = 0.52$	4 (9%)
Minor protection (3–5 episodes)	11 (25%)	$p = 0.089$	4 (9%)
Failure (>5 episodes)	10 (22.7%)	$p < 0.001$	28 (63.6%)
Total	44	$p = 0.002$	44

Table 3

Analysis of nausea

Grades	Thiethylperazine + methylprednisolone		Thiethylperazine + placebo
0 (No nausea)	11 (25%)	p = 0.43	7 (15.9%)
1 (Slight nausea)	15 (34%)	p = 0.028	5 (11.3%)
2 (Moderate nausea)	9 (20.4%)	NS	9 (20.4%)
3 (Severe nausea)	9 (20.4%)	p = 0.004	23 (52.2%)
Total	44	p = 0.007	44

Table 4

Side-effects

	Thiethylperazine + methylprednisolone	Thiethylperazine + placebo
Dryness of the mouth	30 (68%)	20 (45.4%)
Moderate sedation	13 (29.5%)	11 (25%)
Facial flushing	10 (22.7%)	–
Euphoria	12 (27.2%)	–

The T + MP arm was also superior for control of nausea. Grade 0 nausea was in this arm observed in 25% of the patients compared to 16% in the T + placebo arm. The corresponding percentage for grade 3 nausea were 20% and 52% respectively (Table 3). The patients' preferences (70% preferred the T + MP arm versus 14% the T + placebo arm), were also strikingly in favor of T + MP ($p < 0.001$).

Complete protection against vomiting was somewhat more frequent among women over 54 years of age than among the younger patients (32% vs 21%), but this difference was not statistically significant.

The side-effects due to the antiemetics are shown in Table 4. In the group which received methylprednisolone dryness of the mouth was more frequent (although not statistically significant), while sedation, usually moderate, occurred with similar frequency in both arms. Other side-effects in the group that received methylprednisolone were facial flushing in 10 patients (23%) and euphoria in 12 (27%).

Discussion

Phenothiazines have been the most extensively used agents to prevent chemotherapy induced nausea and vomiting, although their rather low activity generally restricts their use to regimens which are only moderately emetogenic such as fluorouracil. Up to now, the combination of phenothiazines with other antiemetic agents has produced contradictory results concerning emesis induced by doxorubicin-containing regimens (4, 5).

Different trials suggest that corticoids might increase the efficacy of the conventional antiemetic agents not only in patients treated with cisplatin (11–13, 19), but also in those receiving chemotherapy regimens without cisplatin (14–17). The efficacy of dexamethasone in vomiting induced by combinations containing doxorubicin has been assessed only in a few studies (14, 20). With regard to methylprednisolone, its efficacy was comparable to that of metoclopramide in patients who received doxorubicin (18), although it has not been specifically assessed with regard to the FAC treatment.

The present trial suggests that the combination of thiethylperazine and methylprednisolone gives better antiemetic control than thiethylperazine alone in patients treated with FAC. The results confirm the role of corticosteroids for the control of nausea and vomiting induced by non-cisplatin chemotherapy. The total dose of methylprednisolone used was 500 mg. It is, however, possible that smaller doses can have similar effect (15).

The most important side-effects of the combination of thiethylperazine and methylprednisolone were dryness of the mouth, sedation, facial flushing and euphoria. Of these the most bothersome for the patients were the first two, which, however were not significantly more pronounced than after thiethylperazine alone. No case of diabetic decompensation or psychosis were noted.

In conclusion, the combination of thiethylperazine and methylprednisolone was in our trial more efficacious than thiethylperazine alone in the prevention of nausea and vomiting induced by FAC. However, the percentage of complete protection was still low. More active treatment regimens are therefore needed.

ACKNOWLEDGEMENTS

This work was supported by Upjohn Medical Department, Madrid. The authors would like to thank Dr M. Tonato, Perugia, Italy, and Dr M. S. Aapro, Geneva, Switzerland, for revising the manuscript.

Corresponding author: Dr E. Diaz-Rubio, Servicio de Oncología Médica, Hospital Universitario San Carlos, Plaza Cristo Rey s/n. E-28040 Madrid, Spain.

REFERENCES

1. Mitchell EP, Schein PS. Gastrointestinal toxicity of chemotherapy agents. Semin Oncol 1982; 9: 52–64.
2. Plezia MP, Alberts DS. Nausea and vomiting: mechanisms and managements. Clin Oncol 1985; 4: 357–86.
3. Laszlo J. Nausea and vomiting as major complications of cancer chemotherapy. Drugs 1983; 25 (Suppl): 1–7.
4. Martin-Jimenez M, Diaz-Rubio E. Clinical evaluation of the simultaneous blockade of the dopamine D-2, histamine D-1, and muscarinic cholinergic receptors in cancer chemotherapy induced emesis: results of a controlled trial. Cancer Chemother Pharmacol 1986; 18: 168–71.
5. Mellink WA, Blijham GH, Van Deyk WA. Amitriptyline plus fluphenazine to prevent chemotherapy induced emesis in cancer patients: a double-blind randomized cross-over study. Eur J Cancer Clin Oncol 1984; 20: 1147–50.
6. Edge SB, Funkhouser WK, Berkman A, et al. High-dose oral and intravenous metoclopramide in doxorubicin/cyclophosphamide induced emesis. A randomized double-blind study. Am J Clin Oncol 1987; 10: 257–63.
7. Gralla RJ, Tyson LB, Clark RA, Kris MG. An all oral combination antiemetic regimen for patients receiving cytoxan + adriamycin + vincristine (CAV). Proc ASCO 1985; 4: 267.
8. Navari RM, Hennessey B, Perrine GM. Comparison of antiemetics prochlorperazine and metoclopramide in patients receiving doxorubicin chemotherapy. Proc ASCO 1986; 5: 258.
9. Strum SB, McDermed JE, Streng B, McDermot N. Combination metoclopramide (MCP) and dexamethasone (DXM) — an effective antiemetic regimen in outpatients receiving doxorubicin (DOX)-cyclophosphamide (CYC) chemotherapy (CT). Proc ASCO 1984; 3: 105.
10. Buzdar A, Blumenschein G, Smith T, et al. Adjuvant chemoimmunotherapy following regional therapy for isolated recurrences of brease cancer (Stage IV NED). J Surg Oncol 1979; 12: 27–40.
11. Roila F, Tonato M, Basurto C, et al. Antiemetic activity of high doses of metoclopramide combined with methylprednisolone versus metoclopramide alone in cisplatin treated cancer patients: A randomized double-blind trial of the Italian Oncology Group for clinical research. J Clin Oncol 1987; 5: 141–9.
12. Kris MG, Gralla RJ, Tyson LB, et al. Improved control of cisplatin induced emesis high-dose metoclopramide and with combinations of metoclopramide, dexamethasone and diphenhydramine. Results of consecutive trials in 255 patients. Cancer 1985; 55: 527–34.
13. Kris MG, Gralla RJ, Tyson LB, et al. Controlling delayed vomiting: Double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. J Clin Oncol 1989; 7: 108–14.
14. Cassileth PA, Lusk EJ, Torri, S et al. Antiemetic efficacy of dexamethasone therapy in patients receiving cancer chemotherapy. Arch Intern Med 1983; 143: 1347–9.
15. Chiara S, Campora E, Lionetto R, Bruzzi P, Rosso R. Methylprednisolone for the control of CMF induced emesis. Am J Clin Oncol 1987; 10: 264–7.
16. Roila F, Tonato M, Basurto C, Minotti V, Ballatori E, Del Favero A. Double-blind controlled trial of the antiemetic efficacy and toxicity of methylprednisolone (MP), metoclopramide (MTC) and domperidone (DMP) in breast cancer patients treated with i.v. CMF. Eur J Cancer Clin Oncol 1987; 23: 615–7.
17. Roila F, Basurto C, Minotti V, Ballatori E, Tonato M, Del Favero A. Methylprednisolone versus metoclopramide for prevention of nausea and vomiting in breast cancer patients treated with intravenous cyclophosphamide, methotrexate, 5-fluorouracil: A double-blind randomized study. Oncology 1988; 45: 346–9.
18. Basurto C, Roila F, Bracarda S, et al. A double-blind trial comparing antiemetic efficacy and toxicity of metoclopramide versus methylprednisolone versus domperidone in patients receiving doxorubicin chemotherapy alone or in combination with other antiblastic agents. Am J Clin Oncol 1988; 11: 594–6.
19. Aapro MS, Plezia P, Alberto DS, et al. Double-blind cross-over study of the antiemetic efficacy of high dose dexamethasone to metoclopramide in patients resistant to metoclopramide. Cancer Treat Rep 1983; 67: 381–3.
20. Markman M, Sheidler V, Ettinger D, et al. Antiemetic efficacy of dexamethasone. Randomized, double-blind, cross-over study with prochlorperazine in patients receiving cancer chemotherapy. N Engl J Med 1984; 311: 549–52.