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FROM THE DEPARTMENT OF GYNECOLOGIC ONCOLOGY, REGIONSJUKHUSET, S-701 85 ÖREBRO, SWEDEN.

BETAMETHASONE-DIXYRAZINE VERSUS METOCLOPRAMIDE AS ANTIEMETIC TREATMENT IN CANCER CHEMOTHERAPY

B. SORBE and C. HALLÉN

Abstract

In a prospective randomized and double-blind cross-over study betamethasone-dixyrazine was compared with metoclopramide as antiemetic treatment in cisplatin and doxorubicin chemotherapy. Sixty-two consecutive patients without prior experience of chemotherapy entered the study and were followed during 1–4 courses of treatment. Effect parameters were recorded on questionnaires using the visual analog scale for quantification. The median number of courses per patient was 3.0 (range 1–4). Full protection against nausea and vomiting was achieved in 74% with betamethasone-dixyrazine and in 45% with metoclopramide regardless of the chemotherapy regimen employed. With doxorubicin regimens betamethasone-dixyrazine gave full protection in 94% and metoclopramide in 45%. In cisplatin regimens full emetic protection was achieved in 40% with betamethasone-dixyrazine and in 29% with metoclopramide. Adverse reactions were a significant problem with metoclopramide: restlessness 48%, akathisia 26%, parkinsonism 13%, and acute dystonia 3%. One case (3.2%) of parkinsonism was noted as the only extrapyramidal reaction in the dixyrazine group. Various degrees of sedation were noted in 84% during dixyrazine treatment compared with 71% during metoclopramide therapy. Diarrhea was encountered in 48% after high-dose metoclopramide compared with 6% after antiemetic treatment with betamethasone-dixyrazine. Betamethasone-dixyrazine appears to be a promising antiemetic combination with regard to both efficacy and side effects, but further refinement of the regimen is probably possible through dose adjustments and alternative routes of administration.

Key words: Chemotherapy; malignant tumors, doxorubicin, cisplatin, DTIC, mustine, antiemetics, betamethasone-dixyrazine, metoclopramide.

The need for effective antiemetic therapy has increased dramatically in clinical oncology with the advent of new and highly emetogenic drugs (e.g. cisplatin, dacarbazine and doxorubicin) and the more frequent use of heavy combination chemotherapy.

During the 1980's an increasing interest in this problem has resulted in an exponentially growing number of antiemetic trials and reports (13). The results and conclusions have been confusing and contradictory (14), probably because of weaknesses in study design and evaluation of the results. The studied populations have often been heterogeneous both regarding tumor diagnoses and the chemotherapy regimens employed, as well as regarding prior experience of emetogenic chemotherapy.

High-dose metoclopramide (7), dexamethasone (4, 12), and various phenothiazines (5) have been found to be most promising in preventing nausea and vomiting during and after chemotherapy.

Optimum dose schedules, modes of administration, and treatment times have not yet been established and further research is needed.

To compare the combination of betamethasone-dixyrazine, which had been found promising in an open pilot study (high efficacy and few side-effects), with the established high-dose metoclopramide schedule for preventing nausea and vomiting during cisplatin as well as other types of chemotherapy, a trial was set up and performed during the period 1983–85. The phenothiazine derivative dixyrazine has not been used much to prevent chemotherapy-induced nausea and vomiting but it is well-known in psychiatric practice and for the relief of postoperative nausea (8).

Betamethasone may have an advantage over its stereoisomer, dexamethasone, due to lower plasma clearance, less plasma binding and a larger volume of distribution (distributed more into the body tissues) (15).

Material and Methods

During the period from November 1, 1983, to May 31, 1985, 62 consecutive patients without prior experience of

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chemotherapy were randomized (ABAB versus BABA) to a double-blind prospective and repeated cross-over trial. Betamethasone (Betapred, Glaxo Operations UK Ltd., England) 8 mg and dixyrazine (Esucos, UCB S.A., Brussels, Belgium) 10 mg in combination (B) were compared with high-dose metoclopramide (Primperan, H. Lundbeck A/S, Copenhagen, Denmark) 1 mg/kg (A).

The antiemetics were given as 15 min i.v. infusions diluted in 100 ml NaCl 9 g/l, 1/2 h before chemotherapy and then 1 1/2, 3 1/2, and 5 1/2 h afterwards at a total of 4 doses.

The patients were followed during 4 consecutive courses of chemotherapy 4 weeks apart. All patients were observed in the hospital for 24 h after chemotherapy. The efficacy and side effects of treatment were recorded on both patient and nurse questionnaires using 100 mm visual analog scales (5, 6, 13) to estimate the parameters studied (Table 1).

The chemotherapy regimens consisted of cisplatin, doxorubicin, dacarbazine (DTIC) or nitrogen mustard combinations (Table 2). The cisplatin dose ranged from 20 mg/m^2 to 120 mg/m^2 and the doxorubicin dose from 20 mg/m^2 to 75 mg/m^2. The complete dose range intervals were used in an attempt to evaluate a possible dose-response effect regarding nausea and vomiting. The dose level distributions of both cisplatin and doxorubicin were identical in the two randomized groups (A and B).

The different underlying cancer diagnoses are shown in Table 3. Both parametric (t-test) and non-parametric tests (Mann-Whitney's U test) as well as linear regression analysis were employed in the statistical analysis.

Results

The data comprise 62 patients with a median age of 60 (range 18–78) years (Fig. 1). The male-to-female ratio was 13:49. Altogether, 198 cytostatic courses were followed. Betamethasone-dixyrazine was administered during 96 courses and metoclopramide during 102. The maximum number of courses per patient was 4.

Nausea and vomiting were prevented completely in 59.7% of the patients during course 1 for the entire series. The median nausea intensity was 4.0 according to the visual analog scale and the median number of vomiting episodes was 5.0 among those who experienced any degree of nausea and/or vomiting.

Betamethasone-dixyrazine was superior to high-dose metoclopramide and prevented nausea in 74.2% and vomiting in 67.7% compared to 45.2% and 51.6% respectively (Figs 2, 3). These differences were statistically significant (p=0.018, M–W U test).

During treatment with cisplatin or cisplatin combinations, betamethasone-dixyrazine prevented emesis in 40.0% compared with 28.6% for metoclopramide (p=0.279, M–W U test). During treatment with doxorubicin regimens the dixyrazine combination gave full emetic protection in 93.8% compared with 45.0% for high-dose metoclopramide (p=0.004, M–W U test).

When using a linear regression model no correlation between doxorubicin or cisplatin doses and the degree of nausea during course 1 was noted.

Table 1

Items included in questionnaires for patients and nurses used during the study

I. *Questionnaire for patients*	
1. Nausea	VAS (mm)*
2. Vomiting	No. of episodes
3. Diarrhea	No. of episodes
4. Headache	VAS (mm)
5. Dizziness	Yes/No
6. Drowsiness	VAS (mm)
7. Restlessness	VAS (mm)
8. Muscle rigidity	VAS (mm)
9. Tremor	VAS (mm)
10. Treatment preference	Course No.
11. Other symptoms	Specify type
II. *Questionnaire for nurses*	
1. Nausea	VAS (mm)
2. Sedation	VAS (mm)
3. Extrapyramidal side effects	Specify type: Acute dystonia Akathisia Parkinsonism
Antidotes given (type, dose)	

*VAS = visual analog scale (0–100 mm)

Table 2

Types of chemotherapeutic regimens employed. The main emetogenic drugs are indicated

Drug	No. of patients	Percentage
Doxorubicin	37	59.7
Cisplatin	17	27.4
Cisplatin + doxorubicin	5	8.1
DTIC	2	3.2
Mustine	1	1.6
Total	62	100.0

Table 3

Type and distribution of underlying and treated malignancies

Type of malignancy	No. of patients	Percentage
Ovarian carcinoma	29	46.8
Uterine carcinoma	9	14.5
Breast carcinoma	6	9.7
Lymphoma	6	9.7
Head & neck carcinoma	5	8.0
Lung carcinoma	4	6.5
Gastro-intestinal carcinoma	3	4.8
Total	62	100.0

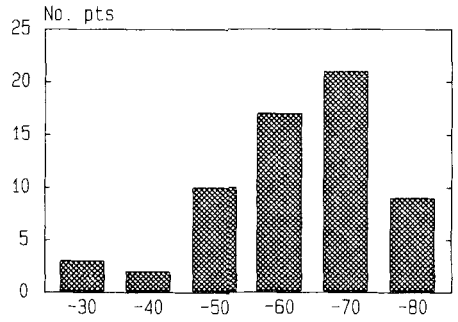

Fig. 1. Age distribution of the whole series (n=62). Median age: 60 (18–78) years.

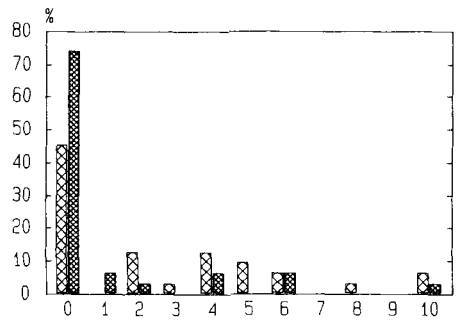

Fig. 2. Intensity of nausea (VAS, cm) during chemotherapy (course 1 day 1), depending on type of antiemetic treatment (betamethasone-dixyrazine (▩) and metoclopramide (▩)).

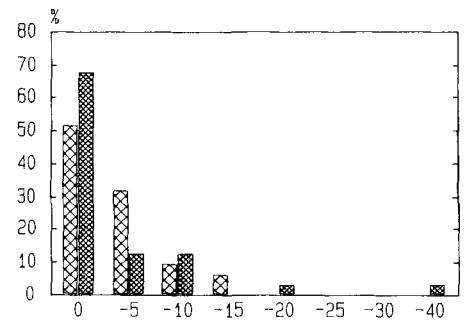

Fig. 3. Number of episodes of vomiting during chemotherapy (course 1), depending on type of antiemetic treatment betamethasone-dixyrazine (▩) and metoclopramide (▩).

Nervousness and restlessness (recorded from the patient questionnaire) was noted in 48.4% of the courses during metoclopramide therapy but in none during betamethasone-dixyrazine therapy. Akathisia was recorded in 25.8% and parkinsonism in 12.9% after metoclopramide, compared to a single case (3.2%) of parkinsonism after dixyrazine administration. Acute dystonic reactions were recorded only during 2 of the 102 metoclopramide courses. The reactions subsided completely following i.v. injection of biperiden 5 mg (Akineton, Knoll AG, Ludwigshafen am Rhein, FRG).

Significant sedation was noted in 84% of the patients treated with betamethasone-dixyrazine compared with 71% of the patients after treatment with high-dose metoclopramide. Diarrheas (two or more bowel movements in 24 h) was recorded during 48.4% of the metoclopramide courses compared with 6.5% of the dixyrazine courses.

Discussion

In this series of patients with no prior experience of chemotherapy the betamethasone-dixyrazine combination was superior to conventional high-dose metoclopramide in preventing nausea and vomiting. This was especially true of doxorubicin regimens but also applied, even if to a lesser extent, to cisplatin. Protection against vomiting per se during and after cisplatin infusion was the same for the two antiemetic regimens (30.0% versus 28.6%). This means that metoclopramide has a relatively greater antivomiting than antinausea effect compared to betamethasone-dixyrazine, at least during cisplatin chemotherapy.

Nervousness, restlessness, and akathisia were predominant side effects and they were all associated with metoclopramide treatment. Increased bowel movements with clinical diarrheas in 48% of the courses were also a bothersome side effect of high-dose metoclopramide due to inconvenience to the patient, risk of dehydration and increased cisplatin toxicity. The only significant problem with betamethasone-dixyrazine was sedation (84%), and occasionally a slight tendency to confusion, which the patients sometimes found unpleasant. These side-effects were probably related to the dixyrazine component of the combination. No adverse reactions related to betamethasone were recorded. Dixyrazine (8) is a promising, but not frequently used, phenothiazine derivative for the treatment of chemotherapy-induced nausea and vomiting. Further improvement in the dose levels may be possible, perhaps through increased doses and continuous infusions with electronic pumps. Preliminary serum concentration studies have indicated that a high and constant level can be achieved by this technique, and this also seems to be important for an optimal antiemetic effect with this drug.

Corticosteroids (dexamethasone or betamethasone) are important antiemetics, both as single drugs (4, 12, 17) and in combination with other potent antiemetic agents (1, 9). The betamethasone dose (8 mg) used in our study may have been too low and an increase to, for instance, 20 mg may further increase the antiemetic efficacy of the betamethasone-dixyrazine combination.

For cisplatin-induced nausea, high-dose metoclopramide probably constitutes an important part of an antiemetic regimen also containing a corticosteroid (dexamethasone or betamethasone), an anticholinergic drug (diphenhydramine or biperiden) and, perhaps, a diazepam preparation (lorazepam) (1–3, 9, 10). As a single drug, it is less suitable depending on poor antiemetic efficacy and an

unacceptably high rate of extrapyramidal side effects and diarrhea.

To avoid the accumulation of metoclopramide that occurs with repeated i.v. bolus doses, administration of high-dose metoclopramide, consisting of a loading dose followed by a continuous infusion up to 24 h, might also be of interest, at least for in-patients (16).

This study also indicates that the antiemetic therapy should be adjusted to the chemotherapy regimen used and that probably *one* effective regimen for *all* occasions cannot be found.

Request for reprints: Dr Bengt Sorbe, Department of Gynecologic Oncology, Regionsjukhuset, S-701 85 Örebro, Sweden.

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