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A RANDOMIZED, DOUBLE-BLIND, CROSS-OVER STUDY COMPARING A LEVOSULPIRIDE-BASED AND A METOCLOPRAMIDE-BASED COMBINATION IN THE PREVENTION OF PROMECE-CYTABOM-INDUCED EMESIS

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ABSTRACT

Background. **To test two different antiemetic regimens for preventing nausea and vomiting in patients with non-Hodgkin's lymphoma (NHL) undergoing systemic chemotherapy (CT) with ProMECE-CytaBOM (P-C).**

Patients and Methods. **Twenty consecutive untreated adult outpatients with histologically confirmed NHL and scheduled to receive P-C chemotherapy were registered in a randomized, double-blind, cross-over study to compare the antiemetic efficacy of a levosulpiride (LS)-based and metoclopramide (MTC)-based regimen.**

Results. **Complete protection from vomiting was recorded in 93% (62/67) of courses with the LS-regimen and in 89% (62/70) with the MTC-regimen (p = 0.428). No nausea was observed in 84% (56/67) of courses with the LS-regimen and in 74% (52/70) with the MTC-regimen (p = 0.183). No differences in prevention of emesis were recorded when patients crossed to the other regimen. Both regimens were well tolerated; however, on day 8 of chemotherapy, when both antiemetic regimens were administered at a higher dose, the LS-based combination showed significantly lower toxicity (p = 0.035).**

Conclusions. **ProMECE-CytaBOM-induced emesis can be prevented in most cases with appropriate, specifically designed antiemetic therapy. Both the LS- and MTC-based combinations resulted in a high percentage of complete protection from emesis. However, the higher incidence of side effects observed with MTC makes the LS-based regimen preferable for patients receiving P-C chemotherapy.**

Key words: emesis, levosulpiride, metoclopramide, non-Hodgkin's lymphoma, ProMECE-CytaBOM

The combination of prednisone, doxorubicin, cyclophosphamide, and etoposide followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue (ProMACE-CytaBOM, P-C)[1] represents a highly effective treatment for patients with aggressive, non-Hodgkin's lymphomas.[2-5]

However, P-C chemotherapy (CT) is associated with several, sometimes dose-limiting side-effects, including myelosuppression, alopecia, mucositis, peripheral neurotoxicity, cardiotoxicity, and emesis.

The emetogenic potential of P-C is mostly due to doxorubicin and cyclophosphamide on day 1, and the association of cytarabine, vincristine, bleomycin and methotrexate on day 8 of each cycle. On the whole, P-C is regarded as a moderately emetogenic chemotherapeutic program, and patients treated with this regimen should be adequately protected against nausea and vomiting. To date, little information is available on the efficacy of antiemetic medications for patients receiving P-C. In a recently published report by the GISL (Gruppo Italiano per lo Studio dei Linfomi) on a series of patients treated with P-C, standard antiemetic protection with metoclopramide (MTC) (Plasil, Lepetit S.p.A., Milano) and promethazine proved ineffective in over

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Table 1. Patient characteristics.

	LEVO		MTC	
	No. of courses	%	No. of courses	%
age (yr)				
50	1	11	3	27
> 50	8	89	8	73
performance status (WHO)				
0	1	12	8	73
1	4	44	2	19
2	4	44	1	8
sex				
male	3	33	4	36
female	6	67	7	64

50% of cases, especially against drugs delivered on day 8.[5]

Levosulpiride (LS) (Levopraid, Ravizza Farmaceutici S.p.A., Milano) is a benzamide compound with a selective dopamine (D2) receptor antagonist that has been seen to be highly effective in the prevention of CT-induced emesis.[6] Moreover, compared to MTC, this sulpiride stereoisomer seems to present a lower toxicity rate with no extrapyramidal reactions.[6]

In an effort to minimize acute nausea and vomiting in patients undergoing chemotherapy with ProMECE-CytaBOM, we designed a double-blind, cross-over study to compare the efficacy and safety of a LS-based and a MTC-based antiemetic combination. We report here the final results of this study, concluded after 20 consecutive patients had been enrolled.

Patients and Methods

Twenty consecutive patients with histologically confirmed, aggressive NHL scheduled to receive P-C chemotherapy were enrolled. The characteristics of these patients are summarized in Table 1. To be included in the study patients had to be at least 18 years of age, have received no prior CT treatments and be expected to receive at least four cycles of P-C. Exclusion criteria included nausea or vomiting or the use of antiemetic agents in the 24 hours before CT, severe concurrent illness or other causes of vomiting, concurrent use of benzodiazepines (except when given for night sedation), and radiotherapy. The study was approved by the local Ethics Committees of participating institutions and all patients gave informed consent.

Study design

In this double-blind, cross-over study patients were randomly assigned to two different antiemetic programs. Patients assigned to Arm A were to receive two initial cycles of a LS-based antiemetic regimen followed by two cycles of MTC-based therapy, while those in Arm B would be given two initial cycles of a MTC-based regimen followed by two cycles of LS-based therapy. According to the study design each patient would be treated with both antiemetic combinations but in a different sequence (LS×2 → MTC×2 or MTC×2 → LS×2.

ProMECE-CytaBOM chemotherapy

Day 1: cyclophosphamide 650 mg/m^2; etoposide 120 mg/m^2; epidoxorubicin 30 mg/m^2; day 8: cytosine arabinoside 300 mg/m^2; bleomycin 5 mg/m^2; vincristine 1.4 mg/m^2; methotrexate 120 mg/m^2; prednisone 60 mg/m^2 orally, day 1-14 (except days 1 and 8 I.V.). ProMECE-CytaBOM was delivered according to the scheme proposed by Fisher *et al*.[1] except for doxorubicin which was replaced at a 20% higher dose by epidoxorubicin. Epidoxorubicin was preferred to doxorubicin in view of its lower cardiac toxicity at the same tumor effectiveness.[7]

Antiemetic regimen

Levosulpiride-regimen → day 1: LS (0.5 mg/kg in 100 cc saline) over 15 minutes, 30 minutes before and 30 minutes after CT; prochlorperazine (10 mg rectally) 30 minutes before CT; day 8: chlordimethyldiazepam (1 mg orally) 45 minutes before CT; LS (1 mg/kg in 100 cc saline) over 15 minutes, 30 minutes before and 30 minutes after CT; promethazine (50 mg intramuscularly) 45 minutes before CT; prochlorperazine (10 mg rectally) 30 minutes before CT.

Metoclopramide-regimen: → same combination of drugs as Arm A, except LS was replaced with MTC at the same dose.

No other antiemetic agents were given during the 24 hours following chemotherapy. Food

Table 2. Protection from nausea.

	Day 1 No. of courses (%)			*Day 8 No. of courses (%)*		
grade of nausea	LEVO	MTC	p	LEVO	MTC	p
none	28 (82)	28 (78)	0.386	28 (85)	24 (71)	0.238
mild	5 (15)	6 (17)		4 (12)	9 (26)	
moderate	–	2 (5)		–	1 (3)	
severe	1 (3)	–		1 (3)	–	

Table 3. Protection from vomiting.

	Day 1 No. of courses (%)			*DAY 8 N. of courses (%)*		
	LEVO	MTC	p	LEVO	MTC	p
CP	33 (97)	33 (92)	0.139	29 (88)	29 (85)	0.345
PP	–	3 (8)		4 (12)	3 (9)	
EP	1 (3)	–		–	2 (6)	

CP: complete protection; PP: partial protection; EP: equivocal protection.

intake was forbidden in the 6 hours following CT administration. Before discharge, patients were asked about the tolerability of the therapy received. Twenty-four hours after the treatment patients were contacted by phone by a member of the research team who recorded the number of emetic episodes, nausea, and any other adverse events.

The efficacy, tolerability and safety of the antiemetic regimens were recorded for each course (day 1 or day 8 of P-C) of chemotherapy.

Response was defined according to the following criteria: complete protection (no emetic episodes), partial protection (one to three emetic episodes), or equivocal protection (four or more emetic episodes). An emetic episode was defined as a single vomit or retching (vomit not producing liquid) or any number of continuous vomits or retching. Patients not responding to the antiemetic regimens (i.e. 5 or more emetic episodes in any day after CT) received rescue medication (dexamethasone 8 mg intramuscularly, repeated every 12 hours as needed) and were removed from the study.

The grade of nausea was assessed using the following scale: none, no nausea; mild nausea, no interference with normal daily life; moderate nausea, interference with normal daily life; and severe, bedridden due to nausea. Nausea is defined as the sensation of imminent vomiting.

All data were analyzed with the Statistical Package for Social Sciences (SPSS).[8] Differences between groups were assessed using the chi-square test or Fisher's exact test. Grades were grouped when there were too few patients with higher grades.

Results

Six patients in Arm A and 7 in Arm B completed the planned four cycles of CT. In addition, 3 patients in Arm A and 4 in Arm B received at least one course of CT.

Twenty-three courses (8 LS and 15 MTC) were not assessable due to reduced doses of the antineoplastic therapy. Thus a total of 137 courses of antiemetic prophylaxis (70 courses on day 1 and 67 courses on day 8) were available for the present analysis.

Nausea

On day 1, no nausea was registered in 82% of the LS-based and 78% of the MTC-based courses, with no statistically significant differences (p=0.386). On day 8, complete protection was achieved in 85% of the LS-based and 71% of MTC-based courses (p=0.238) (Table 2).

Vomiting

On day 1, complete protection from vomiting was observed in 97% of the LS-based and in 92% of the MTC-based courses. Differences were not significant (p=0.139). On day 8, complete protection was recorded in 88% and 85% of the LS and MTC-based courses, respectively (p=0.345) (Table 3).

Complete protection from nausea was observed in 79% (108/137) of all courses, and complete protection from vomiting in 91% (124/137). Complete protection from nausea and vomiting was achieved in 75% (103/137) of all courses.

Table 4. Cross-over evaluation of prophylaxis of ProMECE-CytaBOM-induced vomiting and nausea.

		Day 1		Day 8	
	Cycle	LS (%)	MTC (%)	LS (%)	MTC (%)
CP nausea	1	8 (89)	9 (82)	9 (100)	8 (73)
	2	8 (89)	7 (70)	5 (62)	4 (44)
	3	6 (67)	8 (100)	7 (78)	7 (87)
	4	6 (86)	5 (71)	7 (100)	4 (67)
CP vomiting	1	9 (100)	10 (91)	9 (100)	10 (91)
	2	9 (100)	8 (80)	7 (87)	8 (89)
	3	8 (89)	8 (100)	8 (89)	7 (87)
	4	7 (100)	6 (86)	5 (71)	5 (83)
CP nausea and	1	8 (89)	9 (82)	9 (100)	8 (73)
vomiting	2	8 (89)	6 (60)	5 (62)	4 (44)
	3	6 (67)	8 (100)	6 (67)	6 (75)
	4	6 (86)	5 (71)	5 (71)	4 (67)

Legend: CP: complete protection.

During the first two cycles of P-C no nausea was registered in 76% (58/76) and no vomiting in 92% (70/76) of courses, respectively. Complete protection from nausea or vomiting was achieved in 75% (57/76) of courses. During the third and fourth cycles, complete protection from nausea and vomiting was achieved in 82% (50/61) and 89% (54/61) of courses, respectively; complete protection from nausea or vomiting was achieved in 75% (46/61) of courses.

No nausea was observed in 84% (56/67) of courses with the LS-regimen and in 74% (52/70) of those with the MTC-regimen ($p = 0.183$). As regards emetic episodes, complete protection was recorded in 93% (62/67) of LS-regimen courses and in 89% (62/70) of those with the MTC-regimen ($p = 0.428$).

During the first two cycles 94% of patients treated with LS and 77% of those treated with MTC experienced complete protection; the differences between the groups was not statistically significant ($p = 0.130$). In patients treated with the LS-based combination, a slight decrease in protection from emesis was observed over the courses. During the third and fourth cycles complete protection from nausea and vomiting was observed in 75% of patients treated with LS and in 77% of those treated with MTC; however, cross-over did not modify the efficacy of the antiemetic regimens (Table 4).

Both the LS- and MTC-based antiemetic combinations were well tolerated, and adverse events were mild (Table 5). However, a sub-set analysis showed that on day 8, when antiemetic drugs were used at a higher dose, the LS-based regimen was associated with a statistically significant lower toxicity rate ($p = 0.035$).

Discussion

Controlling of emesis is an important goal in the supportive care of patients with cancer. This randomized, double-blind, cross-over study demonstrated that the combination of chlordimethyldiazepam, prochlorperazine, promethazine, and LS is very effective against ProMECE-CytaBOM-induced nausea and vomiting.

To our knowledge, this is the first study reporting the efficacy of an antiemetic regimen designed specifically for patients undergoing chemotherapy for NHL.

ProMECE-CytaBOM is a moderately emetogenic chemotherapy regimen comparable to other commonly used CT combinations containing an anthracycline and/or cyclophosphamide. In a previous study we reported that a combination of metoclopramide and promethazine failed to control P-C-induced emesis in over 50% of patients.[5] In that report we also observed that drugs administered on day 8 of

Table 5. Adverse events.

	Day 1 No. of events			Day 8 No. of events	
	LEVO	*MTC*	*p*	*LEVO*	*MTC*
Sedation	–	–		1	2
Diarrhea	1	–		–	1
Confusion	–	–		–	1
Extrapyramidal reactions	–	3		–	1
Hot-flushes	1	–		–	1
Agitation	1	1		1	2
Hiccupping	1	1		1	2
Total	4	5	0.790	3	10

ProMECE-CytaBOM were associated with a higher incidence of emesis than those given on day 1, suggesting that the emetogenic potential of the CT combination (cytarabine, vincristine, bleomycin and methotrexate) on day 8 might be schedule dependent. Therefore on day 8 of this study patients were to receive a different antiemetic scheme, with a higher dose of benzamide (LS or MTC) in addition to chlordimethyldiazepam and promethazine.

The complete protection from acute vomiting in 93% of courses achieved with LS and prochlorperazine on day 1, and with chlordimethyldiazepam, LS, prochlorperazine and promethazine on day 8 of ProMECE-CytaBOM should be considered an extremely remarkable result. Indeed, with serotonin receptor antagonists (a newer class of antiemetic agents), the rate of complete protection from emesis in patients treated with cyclophosphamide (≥600 mg/m^2, in combination)- or anthracycline-based regimens usually does not exceed 70-86%.[9-12]

Both levosulpiride, a selective dopamine (D2) receptor antagonist, and MTC have already been reported to be effective agents in the prevention of acute chemotherapy-induced emesis.[6,14] Moreover, LS exerts its antiemetic action without sedation or extrapyramidal reactions, side effects which often complicate the administration of MTC.[14]

In the present study, adverse events with both antiemetic combinations were mild; however, the percentage of patients experiencing side effects differed between the two groups. The number of patients complaining of adverse experiences on day 8 was significantly higher in the MTC group ($p=0.035$). In particular, no patient in the LS group complained of extrapyramidal reactions, whereas 6% of those receiving MTC ($p = 0.148$) experienced such a reaction.

Finally, it must be noted that the cost of the combination used in the present study is very low (less than $3 on day 1 and less than $6 on day 8), far less than that of low-dose serotonin antagonist-based regimens ($44 per day).

In conclusion, the very high complete protection rate, the absence of distressing extrapyramidal reactions, and the low cost make the LS-based regimen particularly recommendable for patients with aggressive NHL as prophylaxis of ProMECE-CytaBOM-induced acute nausea and vomiting.

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