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ANTIEMETIC EFFICACY OF ONDANSETRON AND METOCLOPRAMIDE, BOTH COMBINED WITH CORTICOSTEROID, IN MALIGNANT LYMPHOMA PATIENTS RECEIVING NON-CISPLATIN CHEMOTHERAPY

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The aim of the present study was to compare the antiemetic efficacy of ondansetron (OND) with metoclopramide (MCP), both combined with corticosteroid (CS) in patients with malignant lymphoma. A total of 109 patients with malignant lymphoma receiving their first series of non-cisplatin chemotherapy (CT) (CHOP or MOPP) were divided into prospective, randomized, open and parallel groups and analyzed at two hematological centres at university hospitals in Copenhagen, Denmark. The patients were randomized to receive one of the two following regimens; 1) OND 8 mg/methylprednisolone 80 mg i.v. before CT and OND 8 mg p.o. after 8 h and at bedtime. OND 8 mg tid days 2–3, and 8 mg tid prn days 4–5 and prednisolone 75–100 mg qds days 2–5 and 2) MCP 30 mg/metylprednisolone 80 mg i.v. before CT and MCP 20 mg p.r. after 4 and 8 h respectively. MCP 20 mg p.r. prn days 1–5 and prednisolone 75–100 mg qds days 2–5. In the acute phase OND/CS was superior to MCP/CS in the control of nausea and emesis, resulting in no emesis in 92% of the OND/CS treated group vs. 50% treated with MCP/CS ($p < 0.001$), and no nausea in 79% (OND/CS) vs. 42% (MCP/CS) ($p < 0.001$). The ultimate aim—neither nausea nor emesis—was reached in 77% (OND/CS) vs. 35% (MCP/CS) day 1 ($p < 0.001$). OND/CS is significantly better than MCP/CS in the control of delayed nausea, 81% (OND/CS) vs. 58% (MCP/CS) ($p < 0.026$). Both the OND/CS and MCP/CS regimens are highly effective in the control of delayed emesis, 94% (OND/CS) vs. 85% (MCP/CS) ($p < 0.26$). Adverse events were mild and experienced in 31% of the patients. In the OND/CS group 13% had constipation vs. 8% in the MCP/CS group. Nine percent treated with OND/CS had headaches compared to none treated with MCP/CS ($p < 0.08$). One extrapyramidal reaction was recorded in the MCP/CS group. In malignant lymphoma patients receiving moderately emetogenic CT, the combination of OND and CS was very effective and significantly better than low dose MCP and CS in the control of acute emesis, acute nausea and delayed nausea.

From the patients point of view, nausea and emesis are the most disabling side-effects of chemotherapy (CT) (1), and can ultimately result in refusal of further treatment.

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High-dose metoclopramide (MCP) has been the cornerstone in the treatment of CT-induced nausea and emesis for many years and has been shown to be effective in both cisplatin and non-cisplatin regimens (2, 3). It may, however, be associated with significant toxicity, i.e. dystonia and akatisia, especially in patients under the age of 30 (4). The antiemetic effect of low-dose MCP has not been shown to be significantly better than placebo (5).

Ondansetron (OND) was the first serotonin (5-hydroxytryptamine$_3$) antagonist to be approved, and has been widely investigated in clinical trials. Other serotonin antag-

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Table 1

Response Criteria

Emesis		Nausea	
Complete control:	0 episodes*	None:	No nausea
Major control:	1–2 episodes*	Mild:	Did not interfere with daily activity
Minor control:	3–5 episodes*	Moderate:	Interfered with daily activity
Failure:	>5 episodes*	Severe:	Bedridden due to nausea

* Emetic episode: One or more continuous vomits or retches. After 1 min without vomits or retches a new episode begins.

onists include granisetron, tropisetron and dolasetron. In cyclophosphamide and antracycline combination regimens, OND used as single antiemetic drug has proved to be superior to MCP (6, 7) in treating acute nausea and emesis, and comparable to MCP combination regimens (8) and dexamethasone used as monotherapy respectively (9).

In breast cancer patients receiving moderately emetogenic CT, the combination of OND and dexamethasone is significantly better than MCP and dexamethasone in the control of acute and delayed nausea and emesis over 6 courses of treatment (10).

In patients treated with high-dose cisplatin, the addition of dexamethasone to OND is more effective than OND alone (11). Likewise OND combined with the D_2-antagonist metopimazine is more effective than OND alone in patients receiving moderately emetogenic CT (12).

No studies, however, have been published to assess the role of OND in combination with corticosteroid (CS) in malignant lymphoma patients receiving non-cisplatin CT.

In this randomized study, the antiemetic efficacy and safety of OND in combination with CS was compared to a regimen of MCP and CS, in patients with malignant lymphoma receiving their first course of CT (MOPP or CHOP).

Material and Methods

The study design was open, randomized, in parallel groups and executed at 2 hematological centres. Due to the mode of administration of the antiemetic drugs it was not practically possible to blind the study. Only patients with histologically verified malignant lymphoma were included. They were to receive their first course of CT (MOPP or CHOP). Patients were excluded if any of the following applied: Age under 18 years, pregnancy, gastrointestinal obstruction, central nervous system metastases, severe concurrent illness, treatment with benzodiazepines (except for night sedation), vomiting, treatment with antiemetics within 24 h prior to study start or concurrent radiotherapy.

The trial was conducted according to the guidelines of the Helsinki II declaration, and approved by the regional ethics committees and by the Danish Health Board. All patients gave oral consent after having received both oral and written information.

The patients with non-Hodgkin lymphomas received CHOP (cyclophosphamide 750 mg/m^2 i.v., doxorubicin 50 mg/m^2 i.v., vincristine 1.4 mg/m^2 (max. 2 mg) i.v., methylprednisolone 80 mg i.v. before CT and prednisolone 100 mg daily p.o. days 2–5).

The patients with Hodgkin's disease received MOPP (mechlorethamine 6 mg/m^2 i.v., vincristine 1.4 mg/m^2 (max. 2 mg) i.v., procarbazine 100 mg/m^2 p.o. days 1–7, methylprednisolone 80 mg i.v. before CT and prednisolone 40 mg/m^2 p.o. days 2–7).

After giving fully informed consent, patients were assigned randomly by use of a computer generated list with balanced blocks of 8 patients to receive one of the following two antiemetic regimens: 1) OND 8 mg i.v. before CT followed by 8 mg p.o. tid days 1–3. On days 4–5 OND 8 mg tid was taken only if necessary. 2) MCP 30 mg i.v. before CT followed by 20 mg p.r. after 4 and 8 h. Thereafter only if necessary days 1–5. Corticosteroid was administered as part of the cytostatic treatment as described in chemotherapy regimens. The chosen dose of MCP was the standard antiemetic regimen used in hematological centres in Denmark.

Table 2

Patient characteristics

	Ondansetron	Metoclopramide
Patients		
Randomized*	56	51
Evaluable	52	48
Males/Females	32/20	33/15
Median age (years)		
Males	52	47
Females	58	66
Age range (years)	21–82	18–82
CHOP/MOPP	41/11	38/10

* 109 patients were randomized. Two patients were excluded both from the analysis of efficacy and adverse events: One received by mistake both OND and MCP, and one patient could not be identified.

Table 3

Control of emesis by ondansetron and metoclopramide both combined with corticosteroid in patients treated with non-cisplatin chemotherapy

All (n = 100) Control	Ondansetron (n = 52)				Metoclopramide (n = 48)			
	Complete[1]	Major[2]	Minor[3]	Failure[4]	Complete[1]	Major[2]	Minor[3]	Failure[4]
Day 1	48	2	2	0	24	8	7	9
	92%	4%	4%	0%	50%	17%	15%	18%
Days 2–5	49	1	2	0	41	4	3	0
	94%	2%	4%	0%	85%	8%	7%	0%
Days 1–5	47	2	3	0	23	7	9	9
	90%	4%	6%	0%	48%	15%	19%	19%

1 = 0 episodes; 2 = 1–2 episodes; 3 = 3–5 episodes; 4 = > 5 episodes

A diary card was completed by the patients on each of days 1–5 (retrospectively for the previous 24 h), documenting the number of vomits and retches, the intensity of nausea and doses of antiemetics taken (for definitions see Table 1). At follow up after 1–4 weeks all patients were asked if they had experienced any adverse events, but no questions of specific adverse events were asked.

Statistical analysis

Analyses of nausea and emesis were carried out separately for day 1 (acute nausea and emesis) and days 2–5 (delayed nausea and emesis). For days 2–5, the analysis was based on the worst grade of nausea or emesis on a single day within the period. The χ^2-test with Yate's correction and Fisher's exact test were used to compare the difference in efficacy of the two antiemetic treatments and the frequency of side-effects. $p < 0.05$ was considered statistically significant.

Results

One hundred and nine patients were randomized. Seven patients were excluded from the efficacy analysis because of protocol violation: 3 received other combinations of cytostatic drugs (2 MACOP-B, 1 ABVD), one received perphenazine and one lorazepam, one was under the age of 18 and one did not take OND appropriately. Two patients were excluded both from the analysis of efficacy and adverse events: One received by mistake both OND and MCP, and one patient could not be identified. Thus, 107 patients were evaluable for the assessment of safety and 100 for antiemetic response; 52 received OND and 48 MCP. All had histologically verified malignant lymphoma (Hodgkin's disease (n = 21) and non-Hodgkin lymphoma (n = 79)) and none had previously received CT. None of the patients received concurrent radiotherapy. No significant statistical differences were found between the treatment groups with regard to age, sex or CT regimen (Table 2). Control of emesis and nausea for the patient groups is shown in Tables 3 and 4.

Acute phase: day 1. Complete protection (no emesis, no nausea) was obtained in 40/52 (77%) treated with OND/CS compared to 17/48 (35%) receiving MCP/CS ($p < 0.001$). No emesis was seen in 92% (OND/CS) vs. 50% (MCP/CS) ($p < 0.001$) and no nausea was seen in 79% (OND/CS) vs. 42% (MCP/CS) ($p < 0.001$). No patients receiving OND/CS were considered treatment failures (> 5 emetic episodes), but 9 patients (19%) failed to respond to MCP/CS. No patients treated with OND/CS, but 6 (13%) treated with MCP/CS experienced severe nausea (bedridden due to nausea).

Table 4

Control of nausea by ondansetron and metoclopramide both combined with corticosteroid in patients treated with non-cisplatin chemotherapy

All (n = 100) Control	Ondansetron (n = 52)				Metoclopramide (n = 48)			
	None[1]	Mild[2]	Moderate[3]	Severe[4]	None[1]	Mild[2]	Moderate[3]	Severe[4]
Day 1	41	10	1	0	20	14	8	6
	79%	19%	2%	0%	42%	29%	16%	13%
Days 2–5	42	8	1	1	28	15	3	2
	81%	15%	2%	2%	58%	31%	6%	5%
Days 1–5	39	11	1	1	18	16	7	7
	75%	21%	2%	2%	38%	33%	15%	15%

1 = No nausea; 2 = Did not interfere with daily activity; 3 = Interfered with daily activity; 4 = Bedridden due to nausea

Delayed phase: days 2–5. No significant difference was found between the two treatment groups with regard to delayed emesis, complete control being achieved in 94% (OND/CS) and 85% (MCP/CS). No delayed nausea was achieved in 81% receiving OND/CS vs. 58% receiving MCP/CS ($p < 0.026$).

An intention-to-treat analysis including 107 patients did not change the findings, although the difference in complete control of nausea days 2–5 did not reach statistical significance ($p = 0.085$).

Both regimens were well tolerated. Adverse events were mild and no patients were withdrawn from the study. Minor adverse events were reported in 18 patients (31 events) receiving OND/CS, and in 14 patients (14 events) treated with MCP/CS. The most common adverse events were constipation in 7 (13%) patients (OND/CS) vs. 4 (8%) patients (MCP/CS), and dyspepsia in 10 (18%) patients (OND/CS) vs. 5 (10%) patients (MCP/CS). Five (9%) patients receiving OND/CS experienced headache and none in the MCP/CS group. None of the above differences were statistically significant. One patient, receiving MCP, experienced an extrapyramidal reaction.

Discussion

In this trial OND/CS was superior to MCP/CS in the management of acute emesis, with 92% vs. 50% complete control in patients receiving moderately emetogenic CT. This is at least as good as earlier trials where patients receiving non-cisplatin CT treated with OND alone obtained control rates form 65–82% (6–9).

No acute nausea was recorded in 79% of patients in the OND/CS group vs. 42% in the MCP/CS group. The OND/CS combination appears to be superior to treatment with OND alone reported in earlier non-cisplatin trials where 42–53% had no nausea (6, 7, 9). Our results (acute nausea and emesis) are equal to those found by Soukop et al. (10) in breast cancer patients receiving non-cisplatin CT, and treated with OND or MCP both combined with dexamethasone.

The problem of delayed emesis was managed well in both groups, with complete control rates of 94% (OND/CS) and 85% (MCP/CS). Thus no statistical difference between the two groups was found. Delayed nausea was also effectively controlled. More patients receiving OND/CS did not have nausea compared to MCP/CS, 81% vs. 58%. The explanation for the low incidence of delayed nausea and emesis could be that the combination of CS and either OND or MCP is effective, or that the emetogenic problems days 2–5 are minor. The CS treatment could be the cause of the effective control of delayed nausea and emesis in our trial. Jones et al. (9) reported that dexamethasone alone provided better control of delayed nausea and emesis compared to OND in patients receiving non-cisplatin CT. On the other hand, our results with the combination of OND and CS show higher efficacy rates than those reported by Jones et al. (9) using either OND or dexamethasone alone in the control of delayed emesis and nausea.

Adverse eventes were mild with no significant difference between the groups. In the written information presented to the patients prior to inclusion in the study it was mentioned that OND treatment could be associated with constipation and headache, and that MCP-treated patients could experience diarrhea, restlessness and muscle rigidity. Although this could result in bias toward more adverse events, the rate of headache and constipation in the OND-treated group were comparable to figures earlier reported (13). The low incidence of extrapyramidal reactions in the MCP-treated group was probably partly due to the high median age of the patients and partly to the dose of MCP used.

The superiority of OND/CS in the control of acute emesis and nausea in this trial has to be seen in the light of the known modest antiemetic efficacy of the chosen dose of MCP. The unblinded design of the trial also gives some uncertainty of the interpretation of the results, because of the risk of bias. However, the absolute rate of success with the combination of OND and CS can hardly be explained as a result of a placebo effect. The findings compare well with those observed previously for similar regimens in the control of emesis after non-cisplatin CT in breast cancer patients (10). Our results were obtained by using 24 mg p.o. of OND daily divided in 3 doses. Dicato et al. (14) have shown that 16 mg p.o. daily is as effective as 24 mg p.o. daily.

The combination of OND and CS seems to be a well-tolerated and very effective antiemetic regimen in a hematological patient group receiving moderately emetogenic CT. Our results should be confirmed by a double blind trial.

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REFERENCES

1. Coates A, Abraham S, Kaye SB, et al. On the receiving end—patients perception of the side-effects of cancer chemotherapy. Eur J Cancer Clin Oncol 1983; 19: 203–8.
2. Gralla RJ, Itri LM, Pisko SE, et al. Antiemetic efficacy of high-dose metoclopramide—randomised trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. N Eng J Med 1981; 305: 905–9.
3. Strum SB, McDermed JE, Pileggi J, Riech LP, Whitaker H. Intravenous metoclopramide—prevention of chemotherapy-induced nausea and vomiting. A preliminary evaluation. Cancer 1984; 53: 1432–9.
4. Kris MG, Leslie B, Tyson RN, et al. Extrapyramidal reactions with high-dose metoclopramide. N Engl J Med 1983; 309: 433–4.

5. Gralla JR. Metoclopramide. A review of anti-emetic trials. Drugs 1983; 25(Suppl. 1): 63–73.
6. Kaasa S, Kvaløy S, Dicato MA, et al. A comparison of ondansetron with metoclopramide in the prophylaxis of chemotherapy-induced nausea and vomiting: a randomized, double-blind study. Eur J Cancer 1990; 26: 311–4.
7. Bonneterre J, Chevallier B, Metz R, et al. A randomised double-blind comparison of ondansetron and metoclopramide in the prophylaxis of emesis induced by cyclophosphamide, fluorouracil, and doxorubicin or epirubicin chemotherapy. J Clin Oncol 1990; 8: 1063–9.
8. Levitt M, Warr D, Yelle L, et al. Ondansetron compared with dexamethasone and metoclopramide as antiemetic in the chemotherapy of breast cancer with cyclophosphamide, methotrexate, and flourouracil. N Engl J Med 1993; 328: 1081–4.
9. Jones AL, Hill AS, Soukop M, et al. Comparison of dexamethasone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. Lancet 1991; 338: 483–7.
10. Soukop M, McQuade B, Hunter E, et al. Ondansetron compared with metoclopramide in the control of emesis and quality of life during repeated chemotherapy for breast cancer. Oncology 1992; 49: 295–304.
11. Roila F, Tonato M, Cognetti F, et al. Prevention of cisplatin-induced emesis: a double-blind multicenter randomised crossover study comparing ondansetron and ondansetron plus dexamethasone. J Clin Oncol 1991; 9: 675–8.
12. Herrstedt J, Sigsgaard T, Boesgaard M, Jensen TP, Dombernowsky P. Ondansetron plus metopimazine compared with ondansetron alone in patients receiving moderately emetogenic chemotherapy. N Eng J Med 1993; 328: 1076–80.
13. Smith RN. Safety of ondansetron. Eur J Cancer Clin Oncol 1989; 25(Suppl. 1): S47–S50.
14. Dicato MA, Kaasa S, Campora E, et al. Efficacy of twice daily versus three times daily oral ondansetron in the prevention of chemotherapy induced emesis: A randomised, single-blind, multicentre study. Clinical Oncol 1992; 4: 275–9.