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Randomized crossover study of the antiemetic activity of levonantradol and metoclopramide in cancer patients receiving chemotherapy

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Summary. *In a randomized crossover study 57 cancer patients receiving chemotherapy with high emetic potential were treated with low-dose levonantradol or standard-dose metoclopramide and crossed over to the other antiemetic drug in the next identical chemotherapy cycle. In the 45 patients evaluable for treatment response the antiemetic efficacy of levonantradol was significantly better: 62% had less nausea and 58% less vomiting, as against 11% and 16%, respectively, with metoclopramide. Patient preference for antiemetic treatment was levonantradol in 49% and metoclopramide in 22% of cases. Levonantradol treatment was accompanied by a relatively high incidence of side-effects (71%) compared with metoclopramide (29%). The antiemetic efficacy of each single drug was incomplete in most cases of this trial, and antiemetic combination therapy is recommended for further trials.*

Introduction

Nausea and vomiting is one of the most frequent and distressing acute side-effects of cytotoxic chemotherapy, and sometimes causes patients to abandon potentially curative chemotherapy. Currently available conventional antiemetic drugs are relatively ineffective, so that alternative drugs, among them delta-9-tetrahydrocannabinol and synthetic cannabinoids, have been introduced into clinical trials.

Recently we conducted a pilot study with the synthetic cannabinoid levonantradol hydrochloride in cancer patients who had experienced nausea and vomiting in prior chemotherapy treatments [5]. The good antiemetic effect of 1 mg levonantradol IM (85% of the patients were found to have less nausea and vomiting than with the previous chemotherapy) was limited by a high incidence of side-effects with unpleasant psychological reactions in 40%.

The promising favorable antiemetic effect of levonantradol encouraged us to compare this drug with standard-dose metoclopramide in a randomized crossover study in cancer patients receiving cytostatic agents. Because of the side-effects seen in the prior study the dose of levonantradol was reduced to 0.5 mg.

Patients and methods

Patients with various advanced malignancies without prior chemotherapy entered this trial, which was conducted at one institution. All patients were asked to give their informed consent to participate in this study. Only patients receiving chemotherapy regimens with high emetic potential were included in this study. No brain or spinal irradiation, psychoactive drugs, or other antiemetics were given concomitantly. Patients were randomly assigned to receive either 10 mg metoclopramide or 0.5 mg levonantradol IM 1 h before and 2 and 6 h after chemotherapy as the first antiemetic treatment, and were changed over to the other drug in the next identical cycle. The antiemetic efficacy was evaluated by a standard questionnaire which was completed by the same interviewer throughout the study before chemotherapy and 2, 6, and 24 h thereafter. Nausea was assessed according to a predetermined scale of 1–4 (1, none; 2, mild, activity not affected; 3, moderate, activity affected; 4, severe, prostrate, unable to get out of bed), vomiting was quantified as the number of incidences. The same 1–4 scale was used for recording changes in appetite (1, good, better than normal; 2, normal, same as usual; 3, fair, some solids; 4, poor, liquids only) and patients' overall relief (1, complete relief; 2, moderate relief, better than 50% reduction; 3, slight relief, less than 50% reduction; 4, no relief). Observed or volunteered symptoms suggestive of side-effects were recorded and scored as mild, moderate, or severe. At the end of the trial patients were asked to state their preference for either treatment.

In all, 57 patients (13 female, 44 male) aged 18–73 (median 49 years) entered the study. All patients had advanced carcinomas of the following origin: lung 20, lymphoma 10, soft-tissue sarcoma 9, breast 4, testis 4, melanoma 4, ovary 3, and osteosarcoma, prostate cancer and head and neck cancer one case each. Seven patients completed only one chemotherapy cycle, two received other antiemetic drugs simultaneously, and three were treated by different chemotherapy, so that 45 patients were completely evaluable for two identical chemotherapy cycles. Of these, 24 patients received *cis*-platinum combination chemotherapy and the other patients were treated with dacarbazine (5), ifosfamide (2), and adriamycin-cyclophosphamide combinations (ACO 10, CHOP 4).

The statistical analysis was performed using the Chi-square test at the $\alpha = 5\%$ level, the critical values being corrected by the Bonferroni inequality; the Craddock-Flood modification of the Chi-square test was used in the case of small samples.

Results

Within the first 24 h after chemotherapy the antiemetic effect of three doses of 0.5 mg levonantradol was significantly better than that of three doses of 10 mg metoclopramide (Table 1).

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Table 1. Comparative results of levonantradol/metoclopramide in the prevention of cancer chemotherapy induced nausea and vomiting (n = 45 evaluable patients)

	Levonantradol (L)	Metoclopramide (M)	L = M
Less nausea[a]	28	5	12
Less vomiting[a]	25	8	12
Episodes of vomiting	140	301	
More appetite[a]	22	2	21
Patient preference	22	10	13

[a] Statistical significant difference from the expected value ($P < 0.05$); L = M, same effect for both drugs

Table 2. Cross-over comparison of antiemetic efficacy of levonantradol (L) and metoclopramide (M) within 24 h after chemotherapy (n = 45 evaluable patients; in parentheses *cis*-platinum therapy only: n = 24)

Nausea	Vomiting			
	L better	M better	L = M	
L better	20 (15)	4 (2)	4 (0)	28 (17)
M better	1 (1)	2 (2)	2 (0)	5 (3)
L = M	4 (0)	2 (1)	6 (3)	12 (4)
	25 (16)	8 (5)	12 (3)	

Statistical test of independence:		
Chi-square	= 12.191	(23.082)
Critical value, P-value (uncorrected)	= 0.016	(0.0001)
Corrected according to Bonferroni (Craddock-Flood)	= 14.05	(≈16.7)

Of 45 patients, 28 (62%) had less nausea with levonantradol and only 5 (11%) with metoclopramide therapy. Throughout the trial the 45 patients had 140 episodes of vomiting with levonantradol, but 301 with metoclopramide.The antiemetic superiority of levonantradol is also documented in the contingency table (Table 2).

If we take the subgroup with *cis*-platinum combination therapy separately (Table 2) we can confirm the better antiemetic effect of levonantradol. Changes of appetite during chemotherapy were also documented, and the appetite was found to be better in the levonantradol group in 49% when compared with the identical metoclopramide cycle. Three patients reported an increase of their normal appetite; one patient complained of excessive eating after levonantradol treatment. When the patients were asked to state their preference for antiemetic therapy, 22 of 45 (49%) preferred levonantradol, 10 of 45 (22%) metoclopramide, and 13 of 45 (29%) were undecided. Patient preference was not congruent with the objective measurement of vomiting or the reported nausea. Two patients with less nausea and vomiting while receiving levonantradol preferred metoclopramide, one patient was undecided about his preference, and another patient who reported the same antiemetic response for both drugs also preferred metoclopramide. The antiemetic effect of both drugs studied was incomplete in most cases, and slightly inferior in *cis*-platinum-treated patients. In this subgroup few

Table 3. Toxicity of levonantradol (0.5 mg IM) and metoclopramide (10 mg IM) treatment (n = 45)

Levonantradol (32 of 45 = 71%)	
Somnolence	18
Dizziness	13
Drunkenness	9
Anxiety	2
Local irritation	3
Poor concentration	2
Disorientation	1
Apathy	2
Excessive eating	1
Paresthesias	1
Xerostomia	1
'High'	1
Metoclopramide (13 of 45 = 29%)	
Sedation	8
Weakness	2
Diarrhea	3
Insomnia	1
Deafness	1

patients were free of gastrointestinal symptoms (no nausea 2 of 24 with metoclopramide, 3 of 24 with levonantradol; no vomiting 2 of 24 with metoclopramide, 3 of 24 with levonantradol). While being treated with metoclopramide more patients had severe unpleasant symptoms during chemotherapy (sever nausea: 11 of 45 with metoclopramide, 1 of 45 with levonantradol; more than 10 episodes of vomiting: 12 of 45 with metoclopramide, 4 of 45 with levonantradol). Of 90 chemotherapy cycles only 16 (18%) [4 (18%) MC, 12 (27%) Levo] caused no nausea and 29 (32% [12 (27%) MC, 17 (38%) Levo] no vomiting.

In all, 32 of 45 (71%) of our patients complained of side-effects with levonantradol (Table 3). Usually side-effects of levonantradol were first reported 1–2 h after the first injection and disappeared within 2–3 h. In most cases moderately severe symptoms of somnolence, dizziness and 'drunkenness' were mentioned. Some patients had difficulty in expressing and explaining their state of consciousness ('floating', 'in suspension', 'fainting while fully conscious'). Six patients had severe intolerable psychological side-effects, such as disorientation, apathy, and anxiety. Local irritation after injection and xerostomia were other rare toxicities. The overall toxicity rate of metoclopramide was tolerable (13 of 45, 29%); the main toxic effects being sedation and diarrhea.

Discussion

In this randomized crossover study we found the antiemetic effect of 3 × 0.5 mg levonantradol IM superior to that of 3 × 10 mg metoclopramide IM. This was equally true for the 24 patients treated with *cis*-platinum combinations. Compared with a previous open trial [5] with 3 × 1.0 mg levonantradol (85% better results compared with the previous chemotherapy cycle with different antiemetic drugs) we found the lower dose of 3 × 0.5 mg still more effective in 60%, while the frequency of subjective intolerable psychological side-effects was markedly reduced (13% for 3 × 0.5 mg vs 40% for 3 × 1.0 mg). These results indicate that there is a dose-effect and a dose-toxicity relationship with an optimal repeated dose of 0.5 mg levonantradol IM. Similar results with high toxicity for

the 1.0-mg levonantradol dose and reduction of psychological side-effects for the 0.5 mg dose have been obtained by other authors [2, 3, 6, 7]. Some other studies found acceptable drug toxicity (similar to that with 15 mg tetrahydrocannabinol PO) for the 1.0-mg levonantradol dose [1, 10].

The repeated dose of 10 mg metoclopramide was chosen because this was the standard prophylactic antiemetic treatment at our institute. High doses of metoclopramide (300–400 mg/m^2) have been reported to improve the antiemesis in *cis*-platinum-treated patients [4]. These doses were followed by a high frequency of dyskinetic and extrapyramidal (40%) side-effects in another study [8]. Future studies should find the optimal dose of metoclopramide with acceptable toxicity. In the present trial emesis was not completely controlled in most cases. Only 16 of 45 patients (4 MC, 12 Levo) had no nausea at all and 29 of 45 no episodes of vomiting. As we know that various chemotherapeutic agents may evoke vomiting via different mechanisms [9] we believe that the combination of antiemetic agents with different sites of action (emetic center, chemoreceptor trigger zone, periphery) might improve prophylaxis and treatment of chemotherapy-induced nausea and vomiting.

In conclusion, we believe that the cannabinoid derivate levonantradol cannot be recommended as standard antiemetic treatment, but might be used as an effective drug for use in combination therapy of severe nausea and vomiting, during cancer chemotherapy.

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