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Levonantradol, a New Antiemetic with a High Rate of Side-Effects for the Prevention of Nausea and Vomiting in Patients Receiving Cancer Chemotherapy

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Summary. *Levonantradol, a new antiemetic compound pharmacologically related to the cannabinoids, was given to 17 patients who had experienced severe and protracted nausea and vomiting during previous courses of cancer chemotherapy, and to six patients receiving a first course of strongly emetic cytostatic treatment. Eight patients were partially protected from acute gastrointestinal disturbances. Of the 23 patients, 21 exhibited some toxicity, with six patients exhibiting major affective side-effects and 13 patients complaining of pain at the injection site. Levonantradol is an active antiemetic compound. Due to the rate of side-effects observed in our study however, we would not recommend use of this agent as an antiemetic drug.*

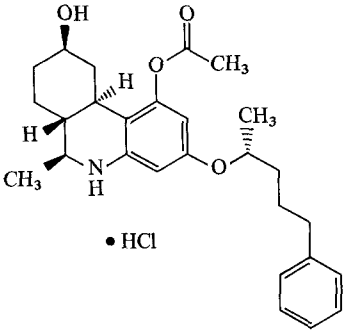

Fig. 1. Structural formula of levonantradol

Introduction

Two-thirds of all patients suffering from cancer experience nausea and vomiting at some time during the course of their disease [10]. Gastrointestinal disturbances remain the most common and most distressing acute side-effects in patients receiving cancer chemotherapy. Current antiemetic treatment remains unsatisfactory, as nausea and vomiting are poorly controlled with standard antiemetic drugs, including antihistamines, phenothiazines, sedatives and tranquilizers. Possible ways of improving our ability to control nausea and vomiting might be (1) a better understanding of the psychological aspects of nausea and vomiting; (2) the better use of currently available antiemetic agents; and (3) the development of new antiemetic agents, such as the cannabinoid-derivatives [6].

Published and anecdotal reports suggest that the ingestion of marijuana before or during antitumor therapy reduces emesis. In prospective randomized trials tetrahydrocannabinol has been shown to be superior to prochlorperazine or placebo in the treatment of chemotherapy-induced nausea and vomiting [9]. In attempts to minimize the cardiovascular and affective effects of tetrahydrocannabinol, several analogs have been synthesized [4, 12]. Levonantradol is the major active isomer of nantradol, a compound pharmacologically related to tetrahydrocannabinol. Its structural formula is shown in Fig. 1. Levonantradol has analgesic and antiemetic properties. Intramuscular adminstration of levonantradol produces consistent blood levels within less than 1 h, which are sustained for at least 4 h [8]. We have tested levonantradol for the prevention of chemotherapy-induced nausea and vomiting in 23 patients treated for various malignancies.

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Patients and Methods

Twenty-three patients received a total of 28 courses of levonantradol. The median age of the 12 female and 11 male patients was 49 years (21–69 years). Seventeen patients had received prior chemotherapy and had experienced severe nausea and vomiting not relieved by conventional antiemetics. Six patients were being treated with a first course of strongly emetic chemotherapy (five patients with *cis*-diammine-dichloroplatinum in single doses of 60–100 mg/m^2, one patient with cyclophosphamide, adriamycin, vincristine, prednisone and bleomycin). Details of the chemotherapy administered and the tumor types treated are shown in Table 1.

To evaluate the effect of the levonantradol therapy, after 24 h the patients were asked for their self-assessment of this new form of antiemetic treatment. Furthermore, the nurses recorded the number of emetic episodes and assessed the antiemetic effect semiquantitatively with the following scoring system:

Symptoms during previous hour	Score
No nausea, no retching, no vomiting	0
Nausea	1
Retching	2
Vomiting	3

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Table 1. Treatment results according to individual patient characteristics

Tumor type	No. pat.	Chemotherapy[a] and dose in (mg/m^2)	Previous chemo-therapy	Assess-ment[b]	Score	No. vomiting episodes	Subjective
Ovarian cancer	1	ADM(30)/DDP(60)	Yes	F	26	20	No relief
	1	DDP(40)	Yes	F	44	30	No relief
	1	DDP(60)	No	F	35	60	–
	3	DDP(80)	No	F	18	2	–
			No	mPR	11	5	–
			No	F	39	9	–
Lung cancer	3	ADM(40)/DDP(20)/VP(80)	Yes	mPR	12	8	Relief
			Yes	MPR	6	4	Relief
			Yes	mPR	12	16	No relief
	1	CTX(1000)/ADM(25)/VP(80)	Yes	F	18	18	No relief
	1	DDP(80)/VP(80)	Yes	F	33	20	No relief
Bladder cancer	1	DDP(100)	No	MPR	4	2	–
Cervical cancer	1	DDP(100)	Yes	F	24	13	No relief
Osteosarcoma	1	CTX(600)/ACTINO(0.5)/BLEO(12)	Yes	F	15	16	No relief
Malignant melanoma	1	DDP(100)/VDS(3)	Yes	F	31	24	No relief
Hodgkin's disease	1	CTX(500)/VLB(6)/ADM(40)	Yes	F	47	12	No relief
	1	CTX(300)/VCR(1)/PCB(100)	Yes	mPR	7	4	Relief
Non-Hodgkin lymphoma	1	CTX(750)/ADM(50)/VCR(1)/BLEO(10)/PRD(50)	No	mPR	8	4	–
	1	CTX(300)/ADM(10)/VCR(1)	Yes	MPR	1	0	Relief
Ovarian cancer	2	Treatment interrupted due to side-effects. Not evaluable for response					
Testicular cancer	1						
Non-Hodgkin lymphoma	1						

[a] ADM, adriamycin; DDP, *cis*-diamminedichloroplatinum(II); VP, etoposide; CTX, cyclophosphamide; ACTINO, actinomycin D; BLEO, bleomycin; VDS, vindesine; VLB, vinblastine; VCR, vincristine; PCB, procarbazine; PRD, prednisone

[b] MPR, major partial response; mPR, minor partial response; F, failure

After each hour the patient was given a score and these were added together for the 24 h period. The antiemetic efficacy was defined as follows:

Response	Score over 24 h
Complete response	0
Major partial response	1–6
Minor partial response	7–12
Failure	> 12

The antiemetic treatment was started 2 h before chemotherapy in the form of an IM injection of levonantradol. The first three patients were given 0.5 mg levonantradol for a body weight of below 50 kg, and 1.0 mg for patients weighing more than 50 kg. The levonantradol dose was repeated every 4 h for a total of five doses. The initial dosage and schedule were based on the recommendations of the manufacturer and early results available from the literature [1, 8]. With two of three patients exhibiting major side-effects at this dose level (one patient with a 'horror trip', one patient with agitation, hyperventilation, and tetanic symptoms), the dose of levonantradol was reduced in the next 20 patients to a starting dose of 0.25 mg; if this dose was well tolerated the patients were given 0.5 mg every 4 h for an additional four injections. Three patients were treated more than one time with levonantradol.

Results

Of 23 patients receiving their first course of levonantradol, 19 are evaluable for antiemetic response. In four patients the antiemetic treatment had to be interrupted after the first or second dose of levonantradol due to intolerable side-effects (three patients due to major affective side-effects with distorted perception of time and space, agitation, and feelings of depersonalization; one patient due to atrial fibrillation). There were 19 evaluable patients, eight of whom (42%) were partially protected from acute gastrointestinal distrubances, with three patients having a major and five patients a minor partial response as defined previously. However, there were no complete responses. The median score for the responders was eight (1–15), and that for the nonresponders 33 (18–47). The responders experienced a median of 4 vomiting episodes (0–16), the non-responders a median of 20 (2–60). Thirteen patients with prior chemotherapy and a full course of levonantradol themselves assessed the antiemetic relief they experienced with this new form of treatment. Of five patients classified as responders, four experienced subjective relief and one felt that nausea and vomiting were about the same as with the previous antiemetic therapy. None of the eight patients classified as non-responders reported subjective improvement with levonantradol as compared with the previous course of treatment. Only two patients treated initially with the higher dose of levonantradol were evaluable for antiemetic response. One patient responded (score 7, four vomiting episodes) and the other experienced no relief from the treatment.

Comparing naive patients with those pretreated with chemotherapy, there were three responders among six patients without prior chemotherapy and five responders among 13 patients with previous cytostatic treatment.

Three patients received more than one course of levonantradol. The first woman with Hodgkin's disease treated with cyclophosphamide, adriamycin, and vinblastine did not respond to the first course of levonantradol (first dose 0.25 mg,

Table 2. Side-effects of levonantradol

Side-effect	Number of patients
Somnolence, fatigue	4/23 (17%)
Major affective side-effects with	6/23 (26%)
Distortion in perception of time and space	1/23
Feelings of depersonalisation	2/23
Hallucinations	3/23
Anxiety	2/23
Agitation	4/23
Hyperventilation	2/23 (9%)
Dizziness	6/23 (26%)
Blurred vision	1/23 (0.5%)
Dry mouth	1/23 (0.5%)
Atrial fibrillation	1/23 (0.5%)
Hypertension	1/23 (0.5%)
Pain at the injection site	13/23 (56%)

subsequent doses 0.5 mg). She was retreated with the same chemotherapy and levonantradol at a dosage level of 1.0 mg every 4 h. She experienced a minor partial response. A second woman with ovarian cancer treated with *cis*-dichlorodiammineplatinum (80 mg/m^2) had a minor partial response to the first course of levonantradol. She was retreated with the identical cytostatic and antiemetic regimen and again had a minor partial response. A third woman with a nodular mixed lymphocytic-histiocytic lymphoma had experienced severe nausea and vomiting during prior courses of chemotherapy. She was treated with adriamycin, cyclophosphamide, and vincristine and nausea and vomiting were significantly reduced with the first course of levonantradol (antimetic score 1, no vomiting episodes). She was treated a second time with the identical cytostatic and antiemetic regimen and again had major partial relief from nausea and vomiting. The patient received levonantradol in the same dosage a third and a fourth time but with doubled doses of the cytostatic agents. The results were then assessed twice as failure, but subjectively she still felt that nausea and vomiting were less pronounced than before the levonantradol therapy.

In our study levonantradol generated considerable side-effects, with 21 of 23 patients exhibiting some toxicity (see Table 2). Thirteen patients (56%) complained of pain at the injection site lasting for about 5 min after administration of the drug. The 23 patients 14 (61%) experienced some form of central nervous system toxicity: six patients exhibited major affective side-effects with distorted perception of time and space, feelings of depersonalization, hallucinations, anxiety, and agitation; six patients complained of dizziness with normal blood pressure, four patients experienced marked somnolence, two patients hyperventilated and developed tetanic symptoms so that the treatment had to be interrupted, and one patient complained of blurred vision. Only two patients had obvious cardiovascular side-effects. One 21-year-old male patient being treated for testicular cancer developed atrial fibrillation 4 h after the first dose of levonantradol (0.25 mg) and 2 h after the administration of *cis*-diamminedichloroplatinum (120 mg/m^2); it lasted for 30 min and converted spontaneously to sinus rhythm after a bout of vomiting. Another patient had raised blood pressure (200/130 mmHg) during an episode of severe agitation and hallucination. None of our patients exhibited any signs of hypotension.

Discussion

In our selected group of patients one would expect that without effective antiemetic treatment all of them would experience severe and protracted nausea and vomiting. Seventeen of these patients had suffered intractable gastrointestinal disturbances during previous courses of cancer chemotherapy, and would have been classified as failures according to the evaluation system we used in the present study. Six patients received a first course of strongly emetic cytostatic treatment. Patients treated with high-dose *cis*-diamminedichloroplatinum for the first time experience nausea for a median of 4.1 h and vomiting for 4 h when treated with placebo or prochlorperazine [2]. These patients would therefore be classified as failures according to our scoring system. Considered in the light of all this, levonantradol showed antiemetic activity in the present study, partially protecting eight of 19 patients from chemotherapy-induced nausea and vomiting. Our results are comparable to those of Kenny and Wilkinson [7] and Smith et al. [11], but less favorable than those reported by Higi et al. [5] and Heim et al. [3]. The possibility that the relatively low dose of levonantradol used in the present study influenced our results unfavorably cannot be refuted. However, preliminary results of Higi and co-workers show that the dose of levonantradol can be reduced to 0.25 mg every 4 h without loss of the antiemetic activity but with a significant reduction of the cannabinoid-like side-effects [5]. In our study we did not observe any obvious difference in the antiemetic activity of levonantradol between patients receiving their first course of cancer chemotherapy and patients with prior exposure to cytostatic treatment. Although our study demonstrates the antiemetic activity of this new compound, levonantradol has a high incidence of side-effects. This has been observed by others [3, 5, 11]. With two of three patients exhibiting major side-effects at the higher dose level used initially (one patient with a horror-trip, one patient with agitation, hyperventilation and tetanic symptoms), we reduced the levonantradol dosage in subsequent patients. But even with the low dosage we frequently observed side-effects. Overall, 14 of 23 patients experienced some form of central nervous system toxicity, with six patients exhibiting major affective side-effects.

In conclusion, levonantradol has activity as an antiemetic compound. However, due to the rate of side-effects observed in our study, we would not recommend the use of this agent as an antiemetic drug.

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