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Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis

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Summary. A prospective randomized double-blind trial comparing the butyrophenone analogue domperidone (D) and the synthetic cannabinoid nabilone (N) in the treatment of cytotoxic-induced emesis was conducted in 38 patients receiving highly emetogenic chemotherapy regimens (70% containing cisplatin). Patients received 20 mg D or 1 mg N the night before chemotherapy and 8-hourly on each chemotherapy day for two consecutive cycles of treatment.

Three of 19 patients randomized to N completed only one cycle because of disease progression (2) or subjectively adverse effects (1). Four of 19 patients completed only one cycle of D because of lack of efficacy (3) or chemotherapy toxicity (1). In all, 32 cycles of N and 33 cycles of D were evaluable for efficacy. The mean number of vomiting episodes in cycle 1 was 4.76 for N and 12.95 for D ($P<0.02$). The corresponding values for cycle 2 were 4.27 and 7.69 ($P>0.10$), and for cycles 1 and 2 combined, 4.53 for N and 10.81 for D ($P<0.01$). Nausea and food intake scores did not differ significantly, although there was a trend towards less nausea and an increased food intake with N. Subjectively adverse effects were more frequent with N and included drowsiness, dizziness, dry mouth, and postural hypotension. N is superior to D for the control of cytotoxic-induced emesis.

Introduction

Nausea and vomiting rank as the most distressing treatment-related effects of cancer chemotherapy [2]. Phenothiazines and conventional doses of the substituted benzamide metoclopramide have proved to be relatively ineffective as antiemetics in this setting [1]. The butyrophenone analogue domperidone (D), the synthetic cannabinoid, nabilone (N), and high doses of metoclopramide have shown more promise. Use of the last drug, however, is limited by the need for hospitalization during therapy and by a significant incidence of dystonic reactions in younger patients [8]. Domperidone, in conventional doses, has shown superior activity over placebo and a very low incidence of side effects [3, 5, 6]. Nabilone has been shown to be more efficacious than placebo, prochlorperazine, or metoclopramide [1]. Although side effects, including drowsiness, dizziness and dry mouth, have been described frequently, in all published trials patients have expressed a preference for N over the comparator.

This study was designed to test the comparative efficacy and side effect profile of D and N in both in- and outpatients receiving a variety of emetogenic regimens, including cisplatin-containing combinations. The trial was of a double-blind, parallel group design. In order to assess the effect of antiemetic treatment over more than one course of chemotherapy, patients were randomized to receive two consecutive courses of the same antiemetic.

Patients and methods

Thirty-eight patients undergoing chemotherapy for advanced malignant disease were randomized to two consecutive cycles of treatment with either D or N, formulated in white capsules of identical appearance. The tumour types are displayed in Table 1. Twenty-three patients were male and fifteen were female, with a mean age of 42 years (range 21–66 years). The chemotherapy regimens remained constant for the two cycles of antiemetic therapy and included cisplatin in 70% of patients, adriamycin in 19%, and ifosfamide in 5% (see Table 2). The design of the anti-emetic therapy administered is shown in Fig. 1. An additional dose of D 20 mg or N 1 mg was administered the night before each cycle of chemotherapy.

Patients completed a diary card and investigators a record form for each day of chemotherapy. Number of vomiting episodes, severity of nausea, and food intake were recorded by the patients and both investigators and patients recorded the side effects of treatment. Erect and supine

Table 1. Patient characteristics: Tumour types

Tumour type	No. of patients
Ovary	11
Testis	9
Bronchus	8
Non-Hodgkin's lymphoma	3
Hodgkin's disease	2
Sarcoma	2
Breast	1
Melanoma	1
Nephroblastoma	1
Total	38

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Table 2. Chemotherapeutic regimens administered during study

Regimen		No. of patients
Cisplatin-containing		
Cisplatin		10
Cisplatin, treosulphan		7
Cisplatin, vincristine, methotrexate, bleomycin		4
Cisplatin, actinomycin D, etoposide		2
Cisplatin, vinblastine, bleomycin		2
Cisplatin, vindesine		1
	Total	26 (70%)
Non-cisplatin-containing		
Adriamycin, bleomycin, vincristine, DTIC		2
Adriamycin, vincristine, cyclophosphamide		2
Adriamycin, vincristine, cyclophosphamide, prednisone		2
Adriamycin, vincristine, etoposide		1
Ifosfamide		2
Vincristine, methotrexate, S-fluorouracil		1
Vindesine, DTIC, CCNU		1
	Total	11 (30%)

Note: Regimen not recorded for one patient

blood pressure and pulse rate measurements were taken 2–4 h after the morning dose of antiemetic.

Treatment efficacy was assessed from the number of vomiting episodes, severity of nausea (0=none; 1=mild; 2=moderate; 3=severe) and food intake (0=none; 1=less than usual; 2=average; 3=more than usual) reported by each patient for the two cycles of therapy.

Results

Nineteen patients were randomized to treatment with N, lone, and nineteen to treatment with D. The number of patients receiving cisplatin- and non-cisplatin-containing regimens was evenly distributed between the two arms. Three patients receiving N completed only one cycle of

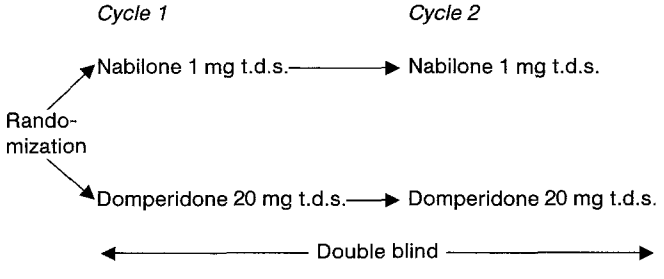

Fig. 1. Study design

Table 3. Reasons for early termination of study

	No. of patients
Lack of efficacy (domperidone)	3
Disease progression	2
Adverse experiences (nabilone)	1
Chemotherapy toxicity	1
Total	7

treatment, because of disease progression in two cases and subjectively adverse response (drowsiness, dizziness, weakness and nausea) to N in one case. Four patients receiving domperidone completed only one cycle, because of lack of efficacy of the antiemetic in three cases and chemotherapy toxicity in one case (see Table 3).

A total of 32 cycles of N and 33 cycles of D were evaluable for vomiting and nausea scores, and 33 cycles of N and 32 of D were evaluable for food intake.

The mean number of vomiting episodes, mean nausea scores and mean food intake scores for patients receiving N compared with patients receiving D are given in Tables 4–6. There were significantly fewer episodes of vomiting reported by patients in the N arm for cycle 1 ($P<0.02$) and for cycles 1 and 2 combined ($P<0.01$) compared with the D arm. For cycle 2 the trend was in favour of N, but it failed to reach statistical significance. It should be noted that one patient with continuous vomiting with D was excluded from the cycle 2 analysis. Nausea scores and food intake scores in the two arms were not significantly different, although the trend favoured N.

Subjectively adverse effects are recorded in Table 7. Drowsiness and dry mouth were reported frequently with both N and D. Dizziness and postural hypotension were more common in the N arm. Other central nervous system effects, including euphoria, confusion, difficulty in talking, and a drunk feeling, were only described with N.

There were no reports of hallucinations. One patient found the side effects associated with N distressing and withdrew from treatment after the first cycle. Three patients receiving N (16%) and four receiving D (21%) reported no adverse effects.

Discussion

In this study, N was statistically superior to D in reducing the frequency of vomiting induced by highly emetogenic cancer chemotherapeutic agents, including cisplatin. The efficacy of N remained constant for two cycles of therapy, with patients experiencing a mean of four to five episodes of vomiting per cycle. With D, the mean vomiting scores in both cycles (12.95 and 7.69, respectively) were similar to those reported for placebo-treated patients [4, 7, 9, 10].

The mean severity of nausea with N was scored as mild to moderate, compared with a moderate score for D. The average food intake with N was less than usual, but lay between none and less than usual on D. These differences did not reach statistical significance.

Subjectively adverse effects, including drowsiness, dizziness, dry mouth and postural hypotension, were more frequent in the N arm, and euphoric and dysphoric side effects were only recorded in association with N therapy. Nevertheless, only one patient discontinued N because of

Table 4. Mean number of vomiting episodes

	Nabilone		Domperidone		*P* value[b]
	Number of evaluable patients	Mean number of vomiting episodes	Number of evaluable patients	Mean number of vomiting episodes	
Cycle 1	17	4.76	19	12.95	<0.02
Cycle 2	15	4.27	14	7.69[a]	>0.10
Cycles 1 and 2	32	4.53	33	10.81[a]	<0.01

[a] Excludes one patient with continuous vomiting on domperidone
[b] Unpaired Student's *t*-test

Table 5. Mean nausea scores

	Nabilone		Domperidone		*P* value[b]
	Number of evaluable patients	Mean score[a]	Number of evaluable patients	Mean score	
Cycle 1	17	1.47	19	2.05	>0.05
Cycle 2	15	1.53	14	1.93	>0.05
Cycles 1 and 2	32	1.50	33	2.00	>0.05

[a] 0=none; 1=mild; 2=moderate; 3=severe
[b] Kolmagorov-Smirnov test

Table 6. Mean food intake

	Nabilone		Domperidone		*P* value[b]
	Number of evaluable patients	Mean score[a]	Number of evaluable patients	Mean score[a]	
Cycle 1	18	1.10	18	0.72	>0.05
Cycle 2	15	1.08	14	0.80	>0.05
Cycles 1 and 2	33	1.09	32	0.75	

[a] 0=none; 1=less than usual; 2=average; 3=more than usual
[b] Kolmagorov-Smirnov test

Table 7. Adverse subjective effects with nabilone or domperidone

Adverse experience	Nabilone ($n=19$)	Domperidone ($n=19$)
Drowsiness	11 (58%)	9 (47%)
Dizziness	11 (58%)	4 (21%)
Dry mouth	10 (53%)	8 (42%)
Postural hypotension	4 (21%)	1 (5%)
Headache	2 (11%)	3 (16%)
Lightheadedness	2 (11%)	1 (5%)
Euphoria	2 (11%)	0
Confusion	1 (5%)	0
Difficulty in talking	1 (5%)	0
Drunk feeling	1 (5%)	0
Weakness	1 (5%)	0
Constipation	1 (5%)	0
Nausea	1 (5%)	0
Dyspepsia	0	1 (5%)

side effects, Three patients discontinued D because of lack of efficacy.

In summary, oral N (1 mg t. d. s) is more effective than oral D (20 mg t. d. s.) in the control of cancer chemotherapy-induced emesis. Domperidone at this dosage may be no more effective than placebo.

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