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A Randomized Trial of Oral Nabilone and Prochlorperazine Compared to Intravenous Metoclopramide and Dexamethasone in the Treatment of Nausea and Vomiting Induced by Chemotherapy Regimens Containing Cisplatin or Cisplatin Analogues

D. CUNNINGHAM,*† C.J. BRADLEY,* G.J. FORREST,† A.W. HUTCHEON,§ L. ADAMS,† M. SNEDDON,* M. HARDING,† D.J. KERR,†‡ M. SOUKOP* and S.B. KAYE†

*Department of Medical Oncology, Royal Infirmary, Glasgow G4 0SF, U.K., †Department of Medical Oncology, University of Glasgow, Glasgow G4 0SF, U.K. and §Department of Medical Oncology, Woodend Hospital, Aberdeen, U.K.

Abstract—*Eighty patients receiving their first course of chemotherapy with regimens containing cisplatin or cisplatin analogues entered this open crossover study comparing nabilone* 2 mg *and prochlorperazine* 5 mg *given orally every* 12 h *for four doses against metoclopramide* 2 mg/kg *loading dose intravenously (i.v.), then* 3 mg/kg *as an (i.v.) infusion over* 8 h *and dexamethasone* 20 mg *(i.v.) over* 3–5 min *at the time of chemotherapy.*

There was complete control of nausea and vomiting in 24 *patients* (32%) *given metoclopramide and dexamethasone compared to* 14 *patients* (19%) *given nabilone and prochlorperazine. For the* 70 *patients who completed the crossover assessment of emesis on a linear analogue scale significantly favoured metoclopramide and dexamethasone* (P = 0.02). *However, there was no overall patient preference for the metoclopramide and dexamethasone combination (nabilone and prochlorperazine* 31 *vs. metoclopramide and dexamethasone* 26; 13 *no preference), because a significant proportion of the patients receiving the cisplatin analogue carboplatin preferred nabilone and prochlorperazine* (16 *vs.* 5; 1 *no preference;* P = 0.013).

For patients receiving cisplatin chemotherapy metoclopramide and dexamethasone remains the antiemetic of choice but for regimens containing carboplatin, nabilone and prochlorperazine is better tolerated and preferred by the patients.

INTRODUCTION

HIGH DOSE metoclopramide is established as one of the most effective antiemetics for the treatment of nausea and vomiting induced by cisplatin [1, 2]. However, to optimize control of emesis, Meyer *et al.* focused attention on the need to obtain a serum level of metoclopramide of at least 850 ng/ml 6 h after cisplatin [3]. We have shown that it is possible to achieve this serum level by giving a loading dose of metoclopramide (2 mg/kg), followed by an intravenous (i.v.) infusion (3 mg/kg) over 8 h [4]. Furthermore, the addition of dexamethasone to metoclopramide has been shown to improve emesis control in patients receiving cisplatin regimens [5]. This combination was therefore selected as appropriate to test against the antiemetic combination of nabilone and prochlorperazine [6]. Nabilone is a synthetic cannabinoid with structural similarities to tetrahydrocannabinoid. Early studies with nabilone confirmed its antiemetic properties though reporting a high incidence of adverse effects, particularly on the central nervous system [7, 8]. However, we have shown that combining nabilone with prochlorperazine reduces the incidence of central nervous system side-effects and results in an effective antiemetic combination for the treatment of emesis induced by chemotherapy regimens which do not contain cisplatin [6].

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Address all correspondence to D. Cunningham, Ludwig Institute for Cancer Research, St Mary's Hospital Medical School, Norfolk Place, London W2 1PG, U.K.

Table 1. Histology and site of primary tumours

Tumour histology	Number of patients
Ovarian adenocarcinoma	31
Testicular teratoma	21
Cervical carcinoma	10
Gastric adenocarcinoma	6
Testicular seminoma	3
Breast adenocarcinoma	2
Others	7
Total	80

Table 2. Details of chemotherapy regimens

Chemotherapy regimen	Number of patients
Cisplatin in combination with an anthracycline	9
Cisplatin in combination with an alkylating agent	23
Cisplatin in combination with an antimetabolite	19
Cisplatin alone	3
Carboplatin and chlorambucil	18
Carboplatin alone	4
JM9	4
Total	80

Therefore, the aim of the present study was to compare the established parenteral antiemetics of choice for cisplatin induced emesis—metoclopramide and dexamethasone—against a new oral antiemetic combination with proven efficacy against regimens which do not contain cisplatin.

PATIENTS AND METHODS

Patients

Eighty patients consisting of 47 females and 33 males with a mean age of 42 years (range 18–68 years) entered this study. All had histologically confirmed cancer and were receiving their first course of chemotherapy. The site of primary tumours are shown in Table 1 and chemotherapy regimens are shown in Table 2. All patients were receiving cisplatin in a dose range of 20–50 mg/m^2. Patients with a history of psychiatric illness or those with a past history of extrapyramidal reactions were excluded. All patients gave full informed consent prior to participation in this trial.

Study design and details of antiemetic treatment

This was a randomized open crossover trial where patients were assigned to nabilone and prochlorperazine or metoclopramide and dexamethasone and crossed on the second course. Nabilone 2 × 1 mg tablets combined with prochlorperazine 1 × 5 mg were given *orally* beginning at least 6 h before chemotherapy and continued every 12 h for three or four doses. The fourth dose of antiemetics was omitted if the patient had experienced complete control of nausea and vomiting. Metoclopramide was given as a 2 mg/kg loading dose in 250 ml of physiological saline administered as an i.v. infusion over 15 min before chemotherapy followed by an i.v. infusion of 3 mg/kg in 500 ml physiological saline over 8 h. Just prior to chemotherapy dexamethasone 20 mg made up to a 10 ml volume with physiological saline was administered i.v. over 3–5 min. (More rapid injection can lead to an unpleasant paraesthesia.)

Assessment of antiemetic efficacy and side-effects

The number of episodes of emesis, duration of vomiting, severity and duration of nausea and any change in appetite were recorded for 24 h following administration of chemotherapy, on an in-patient basis. Side-effects of treatment including sedation, dizziness, dryness of the mouth, dysphoria and extrapyramidal reactions were recorded, and graded none, mild, moderate or severe. All recordings were made by senior nursing staff or medical staff. After each antiemetic course the patient indicated the extent of emesis control by marking a cross on a 10 cm linear analogue scale ranging from 'not at all sick' to 'very sick'. After the second antiemetic course the patient completed a questionnaire to determine preference (if any) for either antiemetic regime and outline reasons for this preference.

Statistics

The Wilcoxon matched-pairs signed ranks rest was used to test the differences in the number of episodes and duration of vomiting, severity and duration of nausea, change in appetite and ranking on the linear analogue scale between the two antiemetic regimens. The binomial test was used to analyse the patient preferences between the two antiemetics. The effect of order of drug on preference was analysed using Fisher's exact test and the chi-squared test.

RESULTS

Ten patients failed to cross-over for the following reasons; change of chemotherapy in five, refusal to co-operate in two, protocol violation in two and extrapyramidal reaction in one. Five of these patients were given nabilone and prochlorperazine and five were given metoclopramide and dexamethasone. Results of emesis control for all patients are shown in Table 3. There was complete control

Table 3. Nausea, vomiting and appetite after antiemetic treatment in all patients. [Figures are numbers (%) of patients]

Symptom	Nabilone and prochlorperazine (n = 75)	Metoclopramide and dexamethasone (n = 75)
Nausea		
None	18 (24)	28 (34)
Mild	22 (29)	23 (31)
Moderate	25 (33)	16 (21)
Severe	10 (13)	8 (11)
Vomiting		
None	20 (27)	41 (55)
Present	55 (73)	34 (45)
Appetite		
Increased	3 (4)	0 (0)
Normal	26 (35)	45 (60)
Solids only	27 (36)	19 (25)
Liquids only	19 (25)	11 (15)

of nausea and vomiting in 24 patients (32%) given metoclopramide and dexamethasone and 14 (19%) of patients given nabilone and prochlorperazine.

For the 70 patients who completed the crossover the median number of episodes of vomiting with metoclopramide and dexamethasone was 3.45 ± 0.78 compared to 3.92 ± 0.54 episodes with nabilone and prochlorperazine ($P = 0.051$). Nausea was prevented in 25 patients (36%) given metoclopramide and dexamethasone and 16 patients (23%) given nabilone and prochlorperazine. This difference was not significant but the scores for emesis on the linear analogue scale were significantly better for metoclopramide and dexamethasone (2.5 ± 0.32) compared to nabilone and prochlorperazine (3.5 ± 0.37), $P = 0.018$. For patients receiving carboplatin there was complete control of nausea and vomiting in nine of 21 (43%) given metoclopramide and dexamethasone and eight of 22 (39%) given nabilone and prochlorperazine. This difference was not statistically significant. With regard to side-effects (see Table 4) the following were significantly more frequent with nabilone and prochlorperazine; dizziness ($P < 0.001$), sedation ($P < 0.01$), dryness of the mouth ($P < 0.001$) and dysphoria ($P < 0.05$). Extrapyramidal reactions were only seen with the metoclopramide and dexamethasone combination.

There was no significant patient preference for either antiemetic (31 vs. 26; 13 no preference) (Table 5). However, for patients given carboplatin, a significant proportion preferred nabilone and prochlorperazine ($P = 0.013$). This was mainly because patients preferred the antiemetic given by the oral route. There was no significant relation between the order of administration of antiemetic and antiemetic preference.

DISCUSSION

This is the only randomized trial in the literature comparing metoclopramide and dexamethasone against nabilone and prochlorperazine. The results show that metoclopramide and dexamethasone is the more effective antiemetic combination.

Surprisingly, this apparent superiority was not translated into a significant patient preference for metoclopramide and dexamethasone combination. There are several reasons for this inconsistency. Perhaps the most important factor is that of the 22 patients who received the cisplatin analogue, carboplatin, 16 preferred nabilone and prochlorperazone. This preference was not simply based upon superior antiemetic efficacy but was influenced by the oral route as being the preferred method of receiving antiemetic therapy by these patients. The method of administration was not important to the patients receiving cisplatin because these patients were also receiving intravenous fluids for hyperhydration. Thus a majority of the patients receiving cisplatin preferred metoclopramide and dexamethasone. Another factor which influenced the preferred choice of antiemetic was the side-effect profile of the antiemetics. Although the side-effects of dizziness, sedation and dryness of the mouth were more frequent with nabilone and prochlorperazine, they did not affect the patients' choice of antiemetic. The only side-effects which influenced the patients' antiemetic preference were dysphoria (one patient) and extrapyramidal reactions. Extrapyramidal reactions, which can be particularly alarming for the patient, were only seen with metoclopramide. These reactions were more frequent and severe, than we encountered using a different schedule, in a similar group of patients [1]. With regard to dysphoria, this larger study has confirmed our

Table 4. Side-effects related to antiemetic treatment in all patients. [Figures are numbers (%) of patients]

Side-effect	Nabilone and prochlorperazine (n = 75)	Metoclopramide and dexamethasone (n = 75)
Sedation		
None	15 (20)	30 (40)
Mild	27 (36)	29 (39)
Moderate	26 (35)	15 (20)
Severe	7 (20)	1 (1)
Dizziness		
None	49 (65)	69 (92)
Mild	17 (23)	6 (8)
Moderate	6 (8)	0 (0)
Severe	3 (4)	0 (0)
Dysphoria		
None	66 (88)	73 (98)
Mild	2 (3)	1 (1)
Moderate	5 (7)	1 (1)
Severe	2 (3)	0 (0)
Extrapyramidal reactions		
None	75 (100)	61 (81)
Mild	0 (0)	1 (1)
Moderate	0 (0)	7 (9)
Severe	0 (0)	6 (8)
Dry mouth		
None	46 (61)	69 (92)
Mild	12 (16)	5 (7)
Moderate	10 (13)	1 (0)
Severe	7 (9)	0 (0)
Blurred vision		
None	71 (95)	71 (95)
Present	4 (5)	4 (5)

Table 5. Details of patients' preference for either antiemetic

Reason for preference	*Preferred antiemetic—all patients*		*Preferred antiemetic—carboplatin only**	
	Nabilone and prochlorperazine	Metoclopramide and dexamethasone	Nabilone and prochlorperazine	Metoclopramide and dexamethasone
Less nausea or vomiting	18	24	8	4
Less sedation	2	—	1	—
Less blurred vision	1	—	1	—
No extra-pyramidal effects	4	—	—	—
No dysphoria	—	1	—	1
Prefer tablets	6†	—	6	—
Total	31	26	16	5

*One patient expressed no preference.
†Four patients had less vomiting with dexamethasone and metoclopramide.

previous report of a low incidence of this side-effect when nabilone is combined with prochlorperazine.

Carboplatin is a relatively new anti-cancer agent which is active against a variety of tumours and may ultimately replace cisplatin, for example, in the treatment of ovarian cancer [9] and testicular teratoma. In general carboplatin is better tolerated than cisplatin and may be given as a relatively short i.v. infusion since there is no need for hyperhydration. As yet there is very little information on the best antiemetic to give with carboplatin but our data suggests that nabilone and prochlorperazine

is an appropriate first-line antiemetic treatment. However, for patients receiving cisplatin, metoclopramide and dexamethasone remain the antiemetic treatment of choice, with the proviso that a significant proportion of patients will still experience nausea or vomiting, and that extrapyramidal reactions can be expected in up to 20% of patients.

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