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A Randomised Multicentre Single Blind Comparison of a Cannabinoid Anti-emetic (Levonantradol) with Chlorpromazine in Patients Receiving their First Cytotoxic Chemotherapy*

ANDREW W. HUTCHEON,†‡ JAMES B. D. PALMER,‡ MICHAEL SOUKOP,§ DAVID CUNNINGHAM,§ COLIN McARDLE,‖ JOHN WELSH,¶ FRASER STUART,¶ GRAEME SANGSTER,¶ STANLEY KAYE,¶ DAVID CHARLTON** and HAYDN CASH**

‡*Departments of Medicine and Clinical Oncology, Royal Infirmary, Aberdeen, U.K., Departments of §Medical Oncology and ‖Surgery, Royal Infirmary, Glasgow, U.K.,¶ Department of Clinical Oncology, University of Glasgow, 1 Horselethill Road, Glasgow, U.K. and **Pfizer Central Research, Sandwich, Kent, U.K.*

Abstract—*One hundred and eight patients selected to receive combinations of highly emetic cytotoxic chemotherapy for malignant disease were included in a study of anti-emetic therapy. The patients were randomly allocated to receive levonantradol* (0.5, 0.75 *or* 1 mg) *or chlorpromazine* (25 mg) *prior to receiving their first course of cytotoxic therapy. The appropriate anti-emetic was administered* 2 hr *prior to the start of chemotherapy,* 2 hr *after chemotherapy and subsequently at* 4-*hourly intervals for a further* 8 hr. *The extent of anorexia, nausea and vomiting along with other side-effects were assessed at regular intervals by physicians and nursing staff during the* 24 hr *following chemotherapy. In addition, a self-assessment questionnaire was completed by the patients. Levonantradol* (0.5 mg) *was superior to chlorpromazine* (25 mg) *as an anti-emetic. Both were reasonably well tolerated, although at this dose of levonantradol* 22% *of patients experienced dysphoric reactions. At higher doses of levonantradol the proportion of patients experiencing these reactions rose to* 50%, *but without a concomitant increase in anti-emetic activity. Neither drug achieved satisfactory control of vomiting in patients receiving combinations containing* cis-*platinum. We conclude that levonantradol* (0.5 mg) *is a more effective anti-emetic than chlorpromazine* (25 mg) *in patients receiving cytotoxic chemotherapy. However, its use cannot be recommended due to its high incidence of unacceptable central nervous system side-effects.*

INTRODUCTION

NAUSEA and vomiting occurs in 80–90% of patients receiving cytotoxic chemotherapy [1]. The control with traditional anti-emetics is often only minimally effective. Sallan and colleagues in 1975 [2] demonstrated that cannabinoid derivatives possessed anti-emetic properties. Subsequent studies demonstrated that delta-9-tetrahydrocannabinol (DTHC) was superior to prochlorperazine [3] and conventional doses of metoclopramide [4]. However, the use of DTHC is limited by side-effects, including euphoria, drowsiness, hallucinations, impairment of memory, temporal disorientation, confusion, depersonalisation and hypotension. In an attempt to maximise anti-emetic activity the synthetic cannabinoids, including levonantradol, have been developed. However, as with natural cannabinoids, unpleasant dysphoric reactions have been the major limiting factor.

The purpose of this study was: (1) to determine whether parenteral levonantradol was a safe and effective anti-emetic in patients with malignant disease receiving cytotoxic drugs for the first time, (2) to determine the optimum dose and (3) to compare the anti-emetic activity with the

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†To whom requests for reprints should be addressed at: Ward 3 Woodend General Hospital, Aberdeen, AB9 2YS, U.K.

traditional anti-emetic chlorpromazine in a single blind randomised trial.

MATERIALS AND METHODS

One hundred and eight in-patients with a variety of malignant disease were considered eligible for the study. All patients were receiving their first course of potentially highly emetic cytotoxic chemotherapy. Pregnant women and patients with a history of psychiatric disturbance or cardiovascular disease were excluded.

Informed consent was obtained from all patients before entry into the study. Patient details are shown in Table 1.

Nineteen per cent of patients received combinations of drugs which contained *cis*-platinum. The remaining patients received a variety of cytotoxic agents, including adriamycin and cyclophosphamide (Table 2).

Identically coded 1-ml ampoules containing either levonantradol (0.5, 0.75 or 1 mg) or chlorpromazine (25 mg) were prepared. Patients were randomly assigned to 1 of 4 treatments. The appropriate anti-emetic was given intramuscularly 2 hr prior to starting chemotherapy, 2 hr after the commencement of chemotherapy and a further 2 doses were given at 4-hourly intervals.

The extent of appetite impairment and nausea was assessed on ordered category scales prior to each dose of anti-emetic therapy. The incidence of vomiting was also recorded. Side-effects were carefully documented by the attending clinical staff. At the end of treatment the patients completed a self-assessment questionnaire, detailing side-effects and efficacy.

Comparisons between groups were performed using the Chi-squared test of proportions.

Table 1. *Patient details*

	Levonantradol			Chlorpromazine
	0.5 mg ($n=27$)	0.75 mg ($n=28$)	1.0 mg ($n=26$)	25 mg ($n=27$)
Sex:				
Male	12	14	10	13
Female	15	14	16	14
Age:				
Mean	50.4	49.0	53.0	48.7
Range	21–72	17–70	25–80	21–80
Body area (m^2):				
Mean	1.67	1.72	1.69	1.70
Range	1.33–1.97	1.27–2.00	1.31–2.20	1.35–1.99

Table 2. *Chemotherapy details*

	Levonantradol			Chlorpromazine
	0.5 mg	0.75 mg	1.0 mg	25 mg
cis-Platinum-containing regimes	3	7	5	5
Fluorouracil, doxorubin, mitomycin	8	9	3	3
Cyclophosphamide, doxorubicin, vincristine	2	2	6	4
Cyclophosphamide, doxorubicin, VP 16	3	3	2	2
Cyclophosphamide, methotrexate, fluorouracil	2	2	3	4
Mustine, vinblastine, procarbazine	2	1	1	1
Other regimens	7	4	6	8

Table 3. Overall evaluation of vomiting, nausea and appetite

	Levonantradol			Chlorpromazine
	0.5 mg ($n=27$)	0.75 mg ($n=28$)	1.0 mg ($n=26$)	25 mg ($n=27$)
Vomiting episodes:				
0	20	11	14	11
1–4	3	11	4	9
5–10	2	5	8	7
10	2	1	0	0
Nausea:				
None	14	8	13	9
Mild	6	14	4	13
Moderate	7	5	6	4
Severe	0	1	3	1
Appetite:				
Good	2	3	1	4
Normal	14	2	9	6
Fair	6	13	6	7
Poor	5	10	9	10

RESULTS

The study randomised 108 patients, and the results are shown in Table 3. Complete relief of vomiting was seen in more patients receiving 0.5 mg levonantradol than the group receiving chlorpromazine ($P<0.05$) and the group receiving 0.75 mg levonantradol ($P<0.01$). A similar pattern was seen in rankings for nausea, although none of the comparisons reached statistical significance. Anorexia was commoner in patients receiving levonantradol 0.75 mg ($P<0.01$). These changes are partially related to this group containing more patients receiving *cis*-platinum. When the results are corrected for this imbalance, the level of significance changes from $P<0.01$ to $P<0.05$. Of the 20 patients receiving *cis*-platinum combination schedules, only 3 experienced complete relief of nausea and vomiting.

Patients were asked if they would take this anti-emetic again to prevent nausea and vomiting. Twenty of the 27 patients (74%) in the low-dose group said they would, as opposed to 46% and 57% of those receiving 0.75 and 1.0 mg levonantradol respectively. Seventy-eight per cent of patients receiving chlorpromazine indicated they would take this drug during future treatments.

Adverse effects

Twenty-one of the 108 patients had no side-effects. Of the remaining 87 patients, 36 did not complete the planned anti-emetic course. These patients were uniformly scattered throughout the 4 groups. Twenty-three of the 36 patients were withdrawn because of side-effects, and there were significantly more withdrawals in the 0.75-mg group than the 0.5-mg group ($P<0.05$). The remaining 13 patients were either asleep or had had a complete response to the anti-emetics.

The toxicity data common to both drugs are shown in Table 4. Dizziness and a sedative effect

Table 5. Adverse effects of levonantradol

Adverse effect	Levonantradol 0.5 mg	0.75 mg	1.0 mg
Hallucinations	2	6	6
Depression	–	2	2
Euphoria	1	3	–
Personality change	1	1	2
Confusion	1	1	1
Convulsions	1	–	–
Muscarinic	1	4	2
Miscellaneous	3	–	3

Table 4. Adverse effects common to both levonantradol and chlorpromazine

	Levonantradol			Chlorpromazine
	0.5 mg ($n=27$)	0.75 mg ($n=28$)	1.0 mg ($n=26$)	25 mg ($n=27$)
None reported	8	3	3	7
Drowsiness, sedation	10	13	9	15
Dizziness	9	16	10	8
Injection site pain	3	3	6	2
Hypotension	1	3	1	2

were the two commonest side-reactions, occurred with equal frequency in all groups and did not seem to be related to the dose of levonantradol. Injection site pain occurred with both drugs, but was commoner with levonantradol. Hypotension occurred in seven patients.

The remainder of the toxicity was seen only in those patients receiving levonantradol (Table 5). Hallucinations occurred in 14 patients, being commoner at the higher dose levels. Of the other side-effects described, personality changes, euphoria, depression and confusion occurred, and were generally commoner at the 0.75-mg dosage level. Miscellaneous side-effects included concentration difficulties, wild dreams, altered perception of time and increased sensitivity to sound. One patient had a grand mal seizure precipitated by severe postural hypotension after 2 doses of 0.5 mg levonantradol.

DISCUSSION

The results of this randomised single blind study suggest that levonantradol (0.5 mg) was a significantly superior anti-emetic to chlorpromazine (25 mg). Of the 20 patients receiving combinations of drugs containing *cis*-platinum, 17 experienced nausea, vomiting and loss of appetite, and in only 8 of the patients were the symptoms mild. However, pre-randomisation stratification for chemotherapy received was not performed, and the 0.75-mg levonantradol group contained a greater number of patients receiving the *cis*-platinum regimes. This may partly explain the differences seen between the 0.5- and 0.75-mg groups.

The use of levonantradol was associated with considerable adverse effects, and generally this toxicity was dose-related. Seventeen per cent of the patients had hallucinations and others had some degree of incoordination and disorientation, which would reduce their ability to carry out normal activities. In addition, one serious adverse reaction occurred with levonantradol requiring medical intervention. One of the patients in the 0.5-mg group had a grand mal seizure precipitated by severe postural hypotension. Subsequent investigations, including scans and EEG, were normal, but in this context it is of concern that seizures have been observed in rats receiving high-dose DTHC over prolonged periods [5].

However, despite the side-effects, 48 of the 81 patients receiving levonantradol (59%) chose to receive the same anti-emetic again during subsequent courses of chemotherapy.

We conclude that levonantradol (0.5 mg) is a more effective anti-emetic than chlorpromazine (25 mg) in patients receiving cytotoxic treatment. This marginal advantage of levonantradol is outweighed by the high incidence of side-effects of which the dysphoric reactions are particularly unacceptable.

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