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A Randomised Trial of Dexamethasone, Lorazepam and Prochlorperazine for Emesis in Patients Receiving Chemotherapy

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To define further the place of dexamethasone in antiemetic combinations, lorazepam, prochlorperazine and placebo (LP) were compared with lorazepam, prochlorperazine and dexamethasone (DLP) in a randomised, double-blind, crossover study. Both patient and observer assessments were documented in 84 patients receiving both cisplatin and non-cisplatin chemotherapy. The addition of dexamethasone significantly reduced the severity of nausea ($P=0.002$) and vomiting ($P<0.0001$), duration of nausea ($P=0.01$) and vomiting ($P=0.002$) and the number of vomiting episodes ($P=0.003$). DLP was the superior regimen in subsets of patients receiving cisplatin and the non-cisplatin chemotherapy. The improvements produced by the dexamethasone regimen were large and of major benefit to our patients. Patients documented significantly improved tolerance to chemotherapy with DLP courses ($P=0.0006$). Overall, significantly more patients preferred DLP ($P<0.0001$). Patient assessments produced results similar to observer assessments but gave a broader understanding of their experience. The addition of dexamethasone to prochlorperazine and lorazepam significantly improved our patients' experience while receiving chemotherapy.
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INTRODUCTION

NAUSEA AND VOMITING are most distressing side-effects for patients receiving cytotoxic chemotherapy. Recently, an increasing number of clinical studies have combined antiemetics including lorazepam, prochlorperazine, dexamethasone and high-dose metoclopramide with encouraging results [1–4]. However, more effective antiemetic combinations are required.

Dexamethasone has proven antiemetic effects in a number of clinical studies [5–8]. The combination of prochlorperazine and dexamethasone improved the antiemetic effect compared to prochlorperazine alone [5]. In combination with nabilone, dexamethasone significantly reduced the number of vomiting episodes compared with nabilone alone [6]. When added to high dose metoclopramide, dexamethasone improved control of emesis compared to metoclopramide in some studies but not another [7–9]. Optimal combinations incorporating dexamethasone are yet to be established.

Lorazepam is a minor tranquiliser of the benzodiazepine group which we have previously reported to be superior to prochlorperazine alone when used with prochlorperazine [3, 10]. Prochlorperazine and lorazepam significantly reduced the severity and duration of nausea, the severity of vomiting and the number of vomiting episodes compared with prochlorperazine plus placebo. The combination of prochlorperazine plus lorazepam was easy to administer since it was given without the need for the intravenous line required with high-dose metoclopramide.

In this randomised, double-blind study, we have attempted to improve on our previously reported two-drug combination by studying the addition of dexamethasone. We compared lorazepam and prochlorperazine plus placebo (LP) with the same two drugs plus dexamethasone (DLP).

PATIENTS AND METHODS

Patients

All adult cancer patients who were to receive two consecutive highly emetogenic chemotherapy courses were eligible. The cytotoxic drugs received included cisplatin, doxorubicin, daunorubicin, mustin, actinomycin D, cyclophosphamide, dacarbazine and mitomycin alone or in combination. Patients with a past history of mental illness, diabetes or prior adverse reactions to benzodiazepines or prochlorperazine were ineligible. Patients with significant respiratory disorders were excluded. Patients without prior chemotherapy were preferred.

Study design

Patients were randomised to receive lorazepam, prochlorperazine and placebo (LP) or prochlorperazine, lorazepam and dexamethasone (DLP) for the first study course and crossed over to the alternate regimen for the second course. The study was double-blinded with syringes containing placebo or dexamethasone indistinguishable except by a code number recorded in pharmacy. The study protocol was written to comply with the Guidelines on Human Experimentation established by the National Health and Medical Research Council of Australia and was approved by the Institutional Ethics Committee. All patients gave written informed consent.

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Doses

All patients received lorazepam 0.05 mg/kg orally (taken to the nearest 1 mg) 30 min prior to chemotherapy and again 8 h later. All patients received prochlorperazine 25 mg given by rectal suppository 30 min before chemotherapy and again strictly every 6 h for 24 h. An intravenous injection of 2 ml normal saline was given as a placebo 30 min prior to chemotherapy and by intramuscular injection 8 h later to patients receiving LP. Dexamethasone 4 mg/m^2 in 2 ml was given intravenously 30 min prior to chemotherapy and by intramuscular injection 8 h later to patients receiving DLP.

Assessment of study parameters

At 24 h following each chemotherapy course, patients completed a questionnaire which assessed individual parameters including the severity of vomiting, duration of vomiting, number of vomiting episodes, severity of nausea, duration of nausea, degree of anxiety, sedation and tolerance, extrapyramidal side-effects, hallucinations and diarrhoea. Course preference was nominated after two courses. Patients graded the severity of vomiting, nausea, anxiety and sedation as none, mild, moderate, severe or very severe. The degree of tolerance was recorded as very well, well, not too badly, poorly or very poorly. Duration of nausea and vomiting were recorded to the nearest hour and the number of vomiting episodes was noted. The nurses caring for the patient in hospital prospectively documented all parameters, with the exception of severity and duration of nausea, patient tolerance and course preference over the first 24 h postchemotherapy. Nurses were asked to record motor restlessness, tremor, oculogyric crises, convulsions or diarrhoea. Both patient and observer assessments were documented independently. Nurses caring for the patients were a small constant group involved with this study. Cumulative data such as the number of vomiting episodes were updated as nursing shifts changed. For other data the worst experience observed was the one noted on the final data base.

Statistical methods

Carry-over effects were tested for, as in Koch [11], by comparing the sum of results in course 1 and course 2 for the 2 randomisation arms using Wilcoxon's rank-sum test. There was no indication of carry-over effects in any of the parameters studied ($P>0.1$) except tolerance ($P=0.02$). Treatment effects were estimated, as in Brown [12], and the significance of such effects was tested for using Wilcoxon's rank-sum test comparing the difference in results between courses for the two randomisation arms [11]. Similarly, period effects were estimated by comparing differences in the LP and DLP courses for the two arms. Thus, tests for differences in effect of treatment are valid whether period effects are present or not. Patient treatment preferences were compared using the above methods by creating a variable with the values -1 if course 1 was preferred, 0 if there were no course preferences and $+1$ if course 2 was preferred. Similarly course preferences were compared by creating a variable with the values -1 if LP was preferred, 0 if there were no treatment preferences and $+1$ if DLP was preferred. The incidence of extra-pyramidal side effects, hallucinations and diarrhoea in the two treatment arms were compared using McNemar's test for paired data. Nurses' and patients' assessments were compared using Wilcoxon's signed-ranks test for paired data. P values given refer to two-tailed tests.

Table 1. Patients' characteristics

	No. of patients
Eligible	84
Sex	
Male	41
Female	43
No prior chemotherapy	61
Prior chemotherapy	23
Diagnosis	
Germ cell tumours	16
Breast cancer	14
Sarcoma	11
Bladder cancer	9
Malignant melanoma	8
Small cell lung cancer	6
Unknown primary cancer	5
Head and neck cancer	4
Other	11
Median age (range, years)	52 (23–75)

RESULTS

84 patients received two consecutive courses (168 courses) of the same dose of cytotoxic chemotherapy and were eligible for analysis (Table 1). 42 patients (50%) were randomised to receive DLP in the first course and 42 to receive LP. 45 patients (54%) received cisplatin containing regimens and 39 non-cisplatin regimens.

Using patient assessments, DLP was associated with significantly less severe vomiting compared with LP ($P<0.0001$, Table 2). The severity of vomiting was significantly reduced with DLP as assessed by nurses ($P=0.003$). Patients recorded a significantly reduced duration of vomiting using DLP ($P=0.002$). For those patients who vomited, vomiting continued for a median of 2 h with DLP and 5 h with LP. DLP significantly reduced the number of vomiting episodes as assessed by both patients ($P=0.0003$) and nurses ($P=0.0002$).

Patients assessed the severity of nausea as significantly less with DLP ($P=0.002$, Table 2). The duration of nausea was significantly less with DLP ($P=0.01$). For those patients who

Table 2. Patient assessments (84 patients)

	None	Mild	Moderate	Severe	Very severe	P
Severity of vomiting						
DLP	36	36	14	13	0	<0.0001
LP	18	26	30	20	6	
Severity of nausea						
DLP	50	26	16	7	1	1.002
LP	35	23	17	22	4	
Anxiety						
DLP	76	19	4	1	0	0.02
LP	61	26	10	4	0	
Tolerance*						
DLP	40	40	16	4	0	0.0006
LP	30	21	38	10	1	

Percentages.

DLP=dexamethasone, lorazepam and prochlorperazine; LP=lorazepam, prochlorperazine and placebo.

*Recorded as very well, well, not too badly, poorly, very poorly.

experienced nausea, nausea lasted for a median of 2 h with DLP and 6 h with LP. The patient's overall experience of both regimens was assessed by grading anxiety and tolerance to both regimens and by nominating a preferred regimen. Patients assessed anxiety as significantly less during DLP courses ($P=0.02$) but nurses did not ($P=0.11$). Patients tolerated DLP courses significantly better ($P=0.0006$). Tolerance was the only factor which demonstrated a significant carry-over effect. There was no significant difference in tolerance reported for the first course although DLP was significantly better tolerated than LP in the second course ($P=0.0001$). Following two courses of therapy, 62% of patients preferred DLP, 11% preferred LP and 27% rated them equal ($P<0.0001$).

The results were generally similar in the subset of patients receiving cisplatin. The severity of vomiting was significantly less with DLP as assessed by patients ($P=0.004$) or nurses ($P=0.04$). The number of vomiting episodes was significantly reduced with DLP as assessed by patients ($P=0.02$) or nurses ($P=0.01$). Patients documented significantly less nausea with DLP ($P=0.03$) and better tolerance ($P=0.02$). Patients receiving cisplatin chemotherapy showed a very strong preference for DLP courses ($P<0.0001$).

In patients receiving non-cisplatin containing chemotherapy, the severity of vomiting (patient assessments $P=0.0009$, nurses $P=0.03$) the number of vomiting episodes (patient assessments $P=0.008$, nurses $P=0.003$), duration of vomiting ($P=0.004$) and the severity ($P=0.03$) and duration ($P=0.004$) of nausea all favoured DLP. DLP courses were tolerated better ($P=0.008$) and were significantly preferred by the patients receiving non-cisplatin chemotherapy ($P=0.0003$).

Toxicity experienced was not significantly different when the regimens were compared. Extrapyramidal symptoms including mild restlessness, occurred in 15% of DLP and 8% of LP courses ($P=0.13$). Diarrhoea was seen in 12% of DLP courses and 23% of LP courses ($P=0.06$). Hallucinations occurred in 6% of DLP courses and 4% of LP ($P=0.73$). Sedation was significantly less marked with DLP as assessed by patients ($P=0.03$) but not by nurses ($P=0.94$).

The results obtained comparing these two regimens were similar when assessed by nurses or by patients. There were no significant differences between the nurses' or patients' assessments of the severity of vomiting ($P=0.16$), The duration of vomiting ($P=0.57$) or the number of vomiting episodes ($P=0.37$). Nurses rated anxiety ($P<0.0001$) and sedation ($P=0.015$) as more marked than did the patients.

All major parameters were tested for period effects. Patients tolerated the first course better than the second course ($P=0.05$). No other significant period effects were observed. 61 patients (73%) had received no prior chemotherapy at study entry. Treatment and period effects were estimated separately for these patients and those with prior chemotherapy. No significant differences were found between these two groups of patients. Only 1 (4%) of the 23 patients who had received prior chemotherapy vomited before the common cohort of their first study course and 5 (22%) experienced mild or moderate pretreatment nausea. 1 (2%) of the 61 patients with no prior treatment vomited before his first course and 3 (5%) experienced pretreatment nausea. By contrast only 2 patients (2%) vomited before their second course of therapy, (1 had received DLP for the first course and 1 LP), and 7 (8%) experienced mild or moderate pre-treatment nausea (3 had received DLP for the first course and 4 LP).

DISCUSSION

Lorazepam relieves free-floating and somatic anxiety, has hypnotic effects, produces amnesia and in comparison to diazepam, has a longer duration of action [13]. Lorazepam significantly improves the antiemetic effect of prochlorperazine [3]. In this double-blind placebo controlled study, we have evaluated the addition of dexamethasone to a previously demonstrated effective antiemetic combination, LP. This new combination incorporates two newer antiemetics, lorazepam and dexamethasone, which were superior when randomly compared to high dose metoclopramide alone for control of vomiting [11].

This study clearly shows that the addition of dexamethasone to prochlorperazine and lorazepam significantly reduces the severity of vomiting, the duration of vomiting, the number of vomiting episodes, the severity and duration of nausea, anxiety and sedation felt during chemotherapy and improves the patient's overall tolerance to both cisplatin and non-cisplatin containing chemotherapy. DLP courses were not only significantly better tolerated by patients, they were also preferred by a highly significant majority of patients both in the cisplatin and non-cisplatin chemotherapy subsets.

Since the intent of antiemetic therapy in general is to improve our patients' tolerance to chemotherapy, the dramatic improvement in this parameter with DLP is an important finding of this study. The improvements in antiemetic effects seen with the addition of dexamethasone were large and of major clinical benefit to our patients suggesting that dexamethasone may benefit any patient with vomiting on any other antiemetic regimens. Dexamethasone has recently been added to the new antiemetic, ondansetron, with an improvement in efficacy [15].

The effective three-drug regimen DLP avoids the necessity for prolonged intravenous administration as is necessary with high dose metoclopramide. It is, therefore, suitable for outpatient use since the postchemotherapy doses can be given at home and for this purpose the dexamethasone dose at 8 hours could be given orally. However, premedication with lorazepam may significantly sedate outpatients so that supervised transport home is essential.

In this study, we collected both patient and observer assessments in parallel, analysed treatment comparisons using both data sets and formally compared the two. Comparisons of the antiemetic efficacy of the two regimens were similar for emetic parameters using objective nurses' or subjective patients' assessments. Patients noted that DLP was associated with significantly less axiety and sedation compared to LP. These differences were not noted by nurses. In general, nurses assessed anxiety and sedation as significantly worse than did the patients. The use of patient assessments allowed us to analyse the additional parameters of severity and duration of nausea, overall tolerance and the preferred antiemetic regimen. These parameters gave us a broader understanding of our patients' experience with this new antiemetic regimen.

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Radiation of Jejunal Interposition in T3–T4 Upper Aerodigestive Tumours

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30 patients with T_3 and T_4 tumours of the upper aerodigestive tract had their tumours resected by pharyngolaryngectomy. This was followed by reconstruction of a gullet or creation of a siphon as a tracheohypopharyngeal shunt for voice restoration with a free jejunal autograft. All patients were treated postoperatively with ^{60}Co gamma radiation, 6 MeV photons or 7.5 to 10 MeV electrons of a β-tron, with a dose of 50–65 Gy in the area of the primary tumour and 50–65 Gy to the neck. 4 patients refused further treatment after a depth dose of between 16 and 32 Gy. Local recurrence occurred in 40% of cases. The survival rate was 36.6% (11/30) after a mean follow-up time of 21.5 months, although 2 patients died of intercurrent diseases without recurrence of their tumours. The results obtained justify active surgical intervention with postoperative irradiation even at an advanced stage of the tumour.
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INTRODUCTION

PATIENTS WITH T_3 and T_4 tumours of the upper aerodigestive tract have a very restricted life expectancy, the severety of which is dependent upon the stage of the tumour [1, 2]. Over and above this, in many cases functional impairment of breathing and swallowing also respresents a severe affliction. The therapeutic measures which can be taken into consideration are surgery and/or radiotherapy (RT) [3–5]. A third option is chemotherapy, although its value is not yet proven in controlled trials [6–8]. Of the various approaches free transplantation of a microvascular anastomosed jejunal section has proved to be effective, to the extent that reconstructive surgery can be carried out immediately after resection of the tumour [4, 5, 9, 10]. Thus enabling a satisfactory solution for speech, swallowing, and aesthetics to be found. In these patients postoperative radiotherapy is carried out not only in order to destroy micrometastases but also to maximise the recurrence free life interval and, in this sense, also enhance the quality of life. Our main question is to investigate whether the radiotherapy is well tolerated by the interposition graft and if functional damages are to be expected.

PATIENTS AND METHODS

A total of 30 patients (27 men and 3 women) with advanced tumours of the oropharynx, hypopharynx and larynx (Table 1)