the national cancer institute. *Int J Radiat Oncol Biol Phys* 1982, 8, 263–273.
12. Ashby MA, Ago CT, Harmer CL. Hypofractionated radiotherapy for sarcomas. *Int J Radiat Oncol Biol Phys* 1986, 12, 13–17.
13. Arbeit JM, Hilaris BS, Brennan MF. Wound complications in the multimodality treatment of extremity and superficial truncal sarcomas. *J Clin Oncol* 1987, 5, 480–488.
14. Stinson SF, DeLaney TF, Greenberg J, *et al.* Acute and long-term effects on limb function of combined modality limb sparing therapy for extremity soft tissue sarcoma. *Int J Radiat Oncol Biol Phys* 1991, 21, 1493–1499.

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A Randomised Cross-over Trial of Antiemetic Therapy for Platinum-based Chemotherapy. Improved Control With an Intensive Multiagent Regimen

Michael Findlay, R. John Simes, Keith Cox, Kim Carmichael, Tien Chey, Ed McNeil and Derek Raghavan

In a partially blinded randomised cross-over trial, 78 patients receiving cisplatinum based chemotherapy were assigned to receive two forms of antiemetic therapy: SAD, a regimen composed of serenace (haloperidol), ativan (lorazepam), and dexamethasone followed by low dose maxolon (metoclopramide) and STADMAX, a regimen composed of scopolamine (hyoscine), tavegyl (clemastine), ativan, dexamethasone and high dose maxolon. Each antiemetic regimen was given in random order, with the first and second cycles of cytotoxic chemotherapy. 66 (85%) patients completed both cycles of antiemetic therapy and were available for the cross-over comparison. Significantly less acute vomiting, as assessed by nurse observer ($P < 0.0001$), and less delayed vomiting, as assessed by patient diary ($P = 0.03$), were seen with STADMAX. In the first 18 h, complete control of vomiting (no episodes) was achieved in 30 (45%) patients with STADMAX compared with 10 (15%) receiving SAD. Overall, major control of emesis (≤ 2 episodes) was achieved in 56 (85%) patients with STADMAX compared with 35 (53%) receiving SAD. Vomiting was also better controlled on STADMAX in the week after this initial 18 hour period based on the 7 day patient diary with no vomiting episodes in 18/65 (28%) on STADMAX vs. 13/65 (20%) on SAD. However, no significant differences in appetite, nausea or vomiting were found when based on linear analogue self assessment (LASA) scales recorded by patients. Significant differences in side effects of the two antiemetic regimens were noted on LASA scales with more dry mouth ($P = 0.01$), blurred vision ($P = 0.03$) and diarrhoea ($P = 0.04$) associated with STADMAX and more restlessness ($P = 0.002$) associated with SAD. Significantly, no episodes of dystonic reactions were seen among patients on either regimen. In the 68 patients who completed both cycles and were in a position to express a preference, 46 (68%) preferred STADMAX compared with only 20 (29%) who preferred SAD ($P = 0.001$), while 2 patients expressed no preference. It is concluded that STADMAX is the preferred regimen to SAD for the control of cisplatinum-related emesis. It has a role, both where specific serotonin 3 antagonists are not available and as a model for building more effective combinations where these agents are available.
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INTRODUCTION

CURRENTLY, NO antiemetic therapy offers patients receiving cytotoxic drug treatment, total freedom from nausea and vomiting [1, 2]. Subjectively, these side effects are amongst the worst experienced by patients having chemotherapy [3]. The use of metoclopramide in high doses [4] has made a significant impact on cytotoxic drug-induced emesis, especially when due to *cis*-dichlorodiammine platinum (cis-DDP). Studies using serotonin 3 receptor antagonists as a single agent have also provided encouraging results [5, 6], however, they have also not achieved total antiemetic control with platinum based chemotherapy. While no single agent antiemetic offers ideal control, various combinations have given better prevention of emesis [2, 7]. Work by Borison and colleagues has lead to a better understanding of the anatomy and physiology of the vomiting reflex [8, 9] although the exact location of the vomiting centre is still not certain. It has been postulated that simultaneous blockage of histamine, muscarinic cholinergic and dopamine receptors, found in high density in the emetic pathway, would lead to increased control of vomiting [10]. Multiple blockade regimens

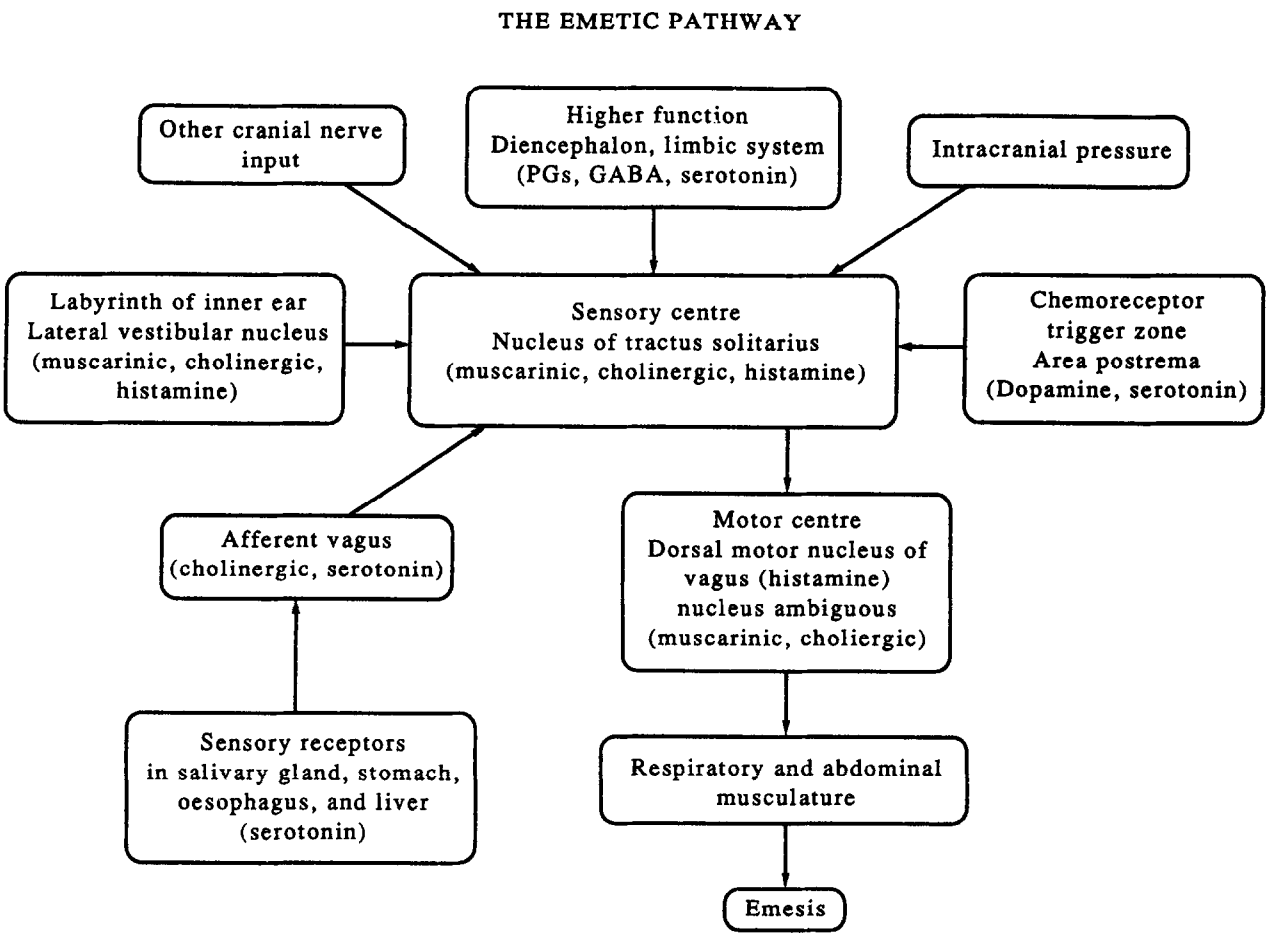

Fig. 1. Various sources of physiological input to the sensory area of the vomiting centre are shown. Information is collated and converted into the motor action of vomiting via the motor centre to the respiratory and abdominal musculature. Where possible the anatomical location and the neurotransmitters involved in this physiological process are documented [8–13]. PGs = prostaglandins; GABA = gamma amino butyric acid.

have been successful in terminating intractable vomiting, resistant to first line treatment [7]. The neurotransmitter model extends to more recent studies localising serotonin 3 receptor densities [11, 12]. Summarised in Fig. 1 is the anatomy of the vomiting reflex arc including the various high density areas of specific neurotransmitter receptors.

Using the neurotransmitter model we designed an antiemetic combination of high dose intensity that would act at the known major receptors without significant respiratory suppression: (i) high dose metoclopramide (at serotonin 3 and dopamine receptors); (ii) hyoscine (at muscarinic cholinergic receptors); (iii) clemastine (at histamine receptors); (iv) dexamethasone (possibly prostaglandin mediated); and (v) lorazepam (possibly gamma amino butyric acid mediated). As selective serotonin 3 antagonists were not yet available in Australia at the time this study was planned, we compared the efficacy of this intensive multireceptor regimen to our previous standard treatment which was of lower dose intensity and acted at fewer sites in the antiemetic pathway [13, 14]. This was with the intention of achieving a best standard treatment that could be compared with or used to improve on serotonin 3 antagonists when they became available.

The two regimens, referred to for brevity as SAD and STADMAX, were tested in a randomised crossover study design with a secondary objective to evaluate the reliability and validity of the measurement instruments.

PATIENTS AND METHODS

Patients

From March 1989 to June 1990, 78 patients with histologically proven cancer were randomised on the trial. All patients were previously untreated and were due to receive cis-DDP based chemotherapy. The minimum cis-DDP dose was 50 mg/m^2 given as a single dose in each treatment cycle. Patients were stratified into two groups according to cis-DDP dose: those receiving < 100 mg/m^2 and those receiving ≥ 100 mg/m^2. This was to ensure patients receiving the higher cis-DDP dose, with the greater emetic potential, were well balanced in the two antiemetic groups.

Specific exclusion criteria for the trial were: age < 18 or > 70 years; previous adverse reactions to any agent in the trial; any antiemetics in the previous 24 h; lung disease or medications predisposing to significant respiratory depression; sleep apnoea

Correspondence to R.J. Simes.
R.J. Simes and T. Chey are at the NHMRC Clinical Trials Centre, Edward Ford Building A27, University of Sydney, NSW 2006; and M. Findlay, K. Cox, K. Carmichael, E. McNeil and D. Raghavan are at the Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050, Australia.
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syndromes; abnormal liver function with bilirubin > 18 mmol/l; cerebral metastases; epilepsy; chronic steroid or psychotropic drug use; pregnancy; and significant prostatism, cardiac rhythm disturbance, glaucoma, or gastric outlet obstruction.

An extra 13 patients, not eligible for the trial, were also registered during the trial period and are included in the reliability and validity assessment of the measurement instruments. The study was carefully explained to each patient and written informed consent was obtained in each case.

Design

Patients were randomly assigned to receive either SAD or STADMAX as the antiemetic regimen with the first cycle of chemotherapy. The alternative regimen was then given with the second cycle of chemotherapy. Random allocation was done using sealed envelopes administered independently of the clinical investigator by a research nurse. Both antiemetic regimens were administered in a single blind fashion. The novel nature of the scopolamine cutaneous patch used in STADMAX was placebo controlled in the SAD regimen by means of a placebo patch. No other placebo controls were used in the study due to the complexities this would have required in treatment administration. Whilst patients were unaware of which antiemetic they were receiving, nursing staff including those completing the nurses' chart were aware of the assigned antiemetic treatment. After completing two cycles of chemotherapy, any patient obtaining benefit from either antiemetic regimen was offered that antiemetic treatment subsequently.

Antiemetic regimens

SAD regimen. This consisted of four active agents: serenace (haloperidol), ativan (lorazepam) and dexamethasone followed by low dose maxolon (metoclopramide). One hour prior to chemotherapy, haloperidol [5 mg intravenous (i.v.) bolus], lorazepam (3 mg orally) and dexamethasone (8 mg i.v. bolus) were given. At the same time, a placebo cutaneous patch was applied behind one ear. After 30 min a second patch was applied behind the other ear. The patches were removed after 3 days. Six hours following the initial drugs, metoclopramide 20 mg was given intravenously every 4 h till 24 h from cis-DDP administration.

STADMAX regimen. This contained five active agents: scopolamine (hyoscine), tavegyl (clemastine), ativan (lorazepam), dexamethasone and the high dose maxolon. A transdermal scopolamine patch (1.5 mg hyoscine with 2.5 cm^2 contact surface area) was applied behind one ear 1 h prior to cis-DDP. Xerostomia, the frequent side effect of scopolamine, was used as the indicator of adequate dosing [15]. If the patient did not complain of a dry mouth or admit to this on indirect questioning, a second scopolamine patch was applied behind the other ear. If xerostomia was evident, then a placebo patch was applied to preserve the blind. Identical questioning was used for both groups. The patches were removed after 3 days. Clemastine, 2 mg was given intravenously 1 h prior to cis-DDP, then eight hourly for two further doses. Lorazepam, 3 mg was given orally 1 h prior to cis-DDP. Dexamethasone, 8 mg was given intravenously 1 h prior to cis-DDP, then 4 mg every 6 h after this for three doses. Metoclopramide as previously described [4], was given at 2 mg/kg in 50 ml of 0.9% NaCl intravenously over 15 min, 1 h prior to cis-DDP and 2, 4, 6 and 9 h subsequently. Thereafter, metoclopramide 20 mg intravenously was given four hourly till 24 h from cis-DDP administration.

Antiemetics after 24 h. Both groups of patients receiving either the SAD or STADMAX regimen received the same antiemetic treatment after the first day. Metoclopramide, 20 mg was given either intravenously or orally every 4 h for 3 days and then after this as needed.

Treatment response. Complete control of emesis was defined as no episodes of vomiting in the first 18 h while overall major control included patients with complete control and those with nearly complete control with 1 or 2 vomiting episodes. No control of emesis was defined as more than five vomiting episodes.

Treatment failure. The indication for second line antiemetic treatment was any patient vomiting more than four times in an hour or more than six times in total. All such patients were treated with prochlorperazine 12.5 mg i.v. every 6 h. Dystonic reactions were to be treated with benztropine, 2 mg i.v. A second dystonic reaction was an indication for withdrawal from the treatment protocol.

Outcome assessment

Nausea, vomiting and side effects were measured both by a nurse observer and by the patient themselves using linear analogue scales and a diary. The nurse observer measured acute nausea and vomiting in the first 18 h, while the patient diary was used to evaluate emesis in the subsequent 7 days. Because of the cross-over design of the trial, patient preferences for each antiemetic were also assessed. Reliability and validity of these measures were also evaluated.

Nurse assessment. The number of vomiting episodes was documented on a bed chart for each 2 h interval from the time of cis-DDP infusion for the following 18 h. Patient sedation was graded on a 5 point scale (1, none; 2, mild, drowsy, wakes to verbal stimulus, orientated; 3, moderate, wakes to physical stimulus, orientated; 4, marked, wakes to physical stimulus, disorientated; 5, severe, unrousable). Other side effects such as dystonic reaction, incontinence, akathisia and diarrhoea were recorded as they occurred.

Patient self assessment. Each patient was given a diary and self report sheet on discharge to return on the day of the next treatment. The first section of the report used linear analogue self-assessment (LASA) scales asking about the amount of nausea and vomiting before and after chemotherapy. For each question patients were asked to mark the level they experienced on a 10 cm line with one end marked "none" and the other end "worst I can imagine". Similar questions regarding appetite and recall of events were asked. The second section of the patient self assessment also used LASA scales for questions regarding possible side-effects of antiemetic therapy: drowsiness, restlessness, confusion, dry mouth, blurred vision, diarrhoea and the thought of having injections or staying in hospital. For each of these symptoms patients were also asked to note the number of days each lasted and complete these sections 7 days after treatment. The third section, in the form of a patient diary, required the person to note the number of vomiting episodes each day and the number of antiemetic tablets taken per day for the next 7 days after the first 18 h period. The patient was also asked to document the number of days until normal eating returned. The fourth section, only administered after two cycles of treatment, asked which of the two treatments was preferred and why.

Reliability and validity assessment. The patient questionnaire was developed by a group of health professionals after an initial pilot on 10 patients. Validation was based on appropriate correlation of different outcome measures, contrasted groups and prediction of patient preferences. Based on an analysis of 83 patients with scores for the first cycle of chemotherapy, patient assessment of vomiting, from LASA scales, correlated reasonably well with appetite (0.38), nausea (0.49) and the patient diary of vomiting (0.48) but not quite as well with the nurse's assessment of vomiting (0.30). Other side effects most often correlated with LASA-rated nausea were confusion (0.38) and restlessness (0.34). Plausible associations were noted for most other measures with reasonable correlations, for example between anticholinergic side effects (blurred vision, dry mouth, etc). Interestingly, restlessness was the symptom most correlated with the thought of injections (0.35) or staying in hospital (0.28).

Test-retest reliability of outcome measures was indirectly estimated by calculating the Pearson correlation coefficient in 38 patients who received the same antiemetic regimen in two adjacent cycles (e.g. second and third cycles). These values will underestimate the true reliability coefficients as they reflect both real fluctuations in vomiting and other outcome measures over time as well as random ones. For assessments of vomiting the coefficient was 0.55 using the nurses' assessment; 0.58 using the patient diary; and 0.42 based on the LASA scale. Estimated reliability coefficients ranged from 0.19 to 0.74 for other LASA measures: nausea, 0.34; appetite, 0.49; drowsiness, 0.19; restlessness, 0.32; confusion, 0.41; dry mouth, 0.56; blurred vision, 0.74 and diarrhoea 0.68.

Statistical analysis

Sample size. A randomised cross-over design was chosen for greater efficiency. The trial was designed to have 80% power of detecting a 15% (15 vs. 30%) difference in the proportion of patients experiencing significant problems of nausea and vomiting using a 2-sided 5% level test. Since outcomes had approximately a 50% correlation between first and second cycles this meant approximately 60 patients were needed.

Analysis. Comparisons within individual patients using a paired *t*-test were used for assessing treatment and period effects while unpaired *t*-tests were employed to test for carry-over effects as described by Hills and Armitage [16]. Equivalent non-parametric Wilcoxon rank tests were used for non-continuous measures. Assessment of patient preferences was based on McNemar's test [17]. Outcomes using LASA scales (measured in mm from the left end of the line) were based on a comparison of single measures between patients except for nausea and vomiting where differences in LASA scales were relative to pre-chemotherapy scores (i.e. post-chemotherapy minus pre-chemotherapy score).

Whilst this study has multiple outcome measures, all individual *P*-values (2-sided) are presented without adjustment for multiple comparisons. Primary outcome measures for the trial were LASA scales of nausea and vomiting, patient diary and nurse's chart of vomiting episodes, and the patients preference for either antiemetic treatment.

RESULTS

Patient and treatment details

Patients. Baseline characteristics of the 78 patients randomised on the trial are shown in Table 1. Median age was 50 years, and approximately half the patients were male (46%). Most patients had a good ECOG performance status with 92% either 0 or 1. Tumour types included ovary, testis, bladder, lung and cervix. Only 15% of the patients had known history of motion sickness although this was unknown in 23%. The two treatment groups were similar in all these respects with no significant differences detected. Information on prior alcohol intake, a recognised prognostic factor in emesis, was not available.

Table 1. Baseline characteristics of randomised patients

Patients' characteristics	Initial treatment SAD	Initial treatment STADMAX	Total
Age			
Median	51.3	48.1	50.0
(Range)	(22.9–70.9)	(24.5–69.8)	(22.9–70.9)
Sex			
Male	19	17	36 (46%)
Female	20	22	42 (54%)
ECOG			
0	26	22	48 (62%)
1	9	14	23 (30%)
2	2	3	5 (6%)
3	2	0	2 (3%)
Tumour			
Ovary	8	7	15 (19%)
Testis	6	6	12 (15%)
Bladder	8	3	11 (14%)
Lung	7	10	17 (22%)
Cervix	6	5	11 (14%)
Other	4	8	12 (15%)
Motion sicknesses			
Yes	5	7	12 (15%)
No	22	26	48 (62%)
Unknown	12	6	18 (23%)

Chemotherapy. Chemotherapy regimens used in these 78 patients are detailed in Table 2. All regimens contained cis-DDP as the single most emetogenic agent. This was usually given first in the combination with the exception of CMV and MVAC where methotrexate ± vinblastine was given on the day before cis-DDP. Any patients vomiting prior to cis-DDP after the methotrexate were not randomised. The two treatment groups were well balanced for cis-DDP dose and chemotherapy regimen.

Patients usually received at least three cycles of cytotoxic chemotherapy. 36 (51%) of evaluable patients had achieved a response to chemotherapy and a further 5 patients had received their chemotherapy as adjuvant treatment.

Antiemetic control

Of the 78 patients randomised, 8 did not complete the first self report form (3 early deaths, 3 missing, 1 patient refusal, 1 overseas) leaving 70 available for group comparisons (Table 3). A further 4 patients did not complete the second treatment form (2 deaths, 1 refusal, 1 no second chemotherapy given) leaving 66 patients available for crossover comparisons of the self report form. 68 patients were able to express a treatment preference (2 of whom had a missing initial self report form).

Table 2. Chemotherapy details of randomised patients

Chemotherapy regimen details	Initial treatment SAD	STADMAX	Total
Cis-DDP ≥ 100 mg/m²			50 (64%)
Cis-DDP, VDE, MitC (PVM)	8	11	19 (24%)
Cis-DDP, VP-16, BLEO (PEB)	6	6	12 (15%)
Cis-DDP, MTX, VBL (CMV)	6	1	7 (9%)
MTX VBL, DOX, Cis-DDP (MVAC)	2	2	4 (5%)
Cis-DDP, FU	3	3	6 (8%)
Cis-DDP	0	2	1 (1%)
Cis-DDP, EPI	0	1	1 (1%)
Cis-DDP < 100 mg/m²			28 (36%)
Cis-DDP	3	4	7 (9%)
Cis-DDP, CLB	5	4	9 (12%)
Cis-DDP, VBL, BLEO (PVB)	5	3	8 (10%)
Cis-DDP, EPI	1	2	3 (4%)
CTX, DOX, Cis-DDP (CAP)	0	1	1 (1%)

Cis-DDP = *cis*-dichlorodiammine platinum; VDE = vindesine; MitC = mitomycin C; VP-16 = etoposide; Bleo = bleomycin; MTX = methotrexate; DOX = doxorubicin; FU = 5-fluorouracil; CLB = chlorambucil.

Group comparisons. Patients receiving lower dose cis-DDP (< 100 mg/m²) experienced less vomiting compared to higher dose (≥ 100 mg/m²) when assessed by LASA scale ($P = 0.02$), (Table 3). Differences in vomiting were less apparent based on the patient diary ($P = 0.09$) and not significant using the nurse's chart ($P = 0.34$). No significant differences in the incidence of

Table 3. Comparison of nausea and vomiting for different risk factors

Item	Mean score (mm or number)		*P*-value
High and low dose of platinum	High ($n = 46$)	Low ($n = 24$)	
Nausea (after–before)	48	43	0.54
Vomiting (after–before)	46	27	0.02
Nurse's chart—acute vomiting	1.9	1.5	0.34
Patient diary—delayed vomiting	7.3	3.5	0.09
Sex	Male ($n = 33$)	Female ($n = 37$)	
Nausea (after–before)	48	45	0.66
Vomiting (after–before)	45	35	0.18
Nurse's chart—acute vomiting	1.9	1.7	0.66
Patient diary—delayed vomiting	6.8	5.2	0.47
Age	Age > 50 ($n = 33$)	Age ≤ 50 ($n = 37$)	
Nausea (after–before)	45	48	0.66
Vomiting (after–before)	39	40	0.98
Nurse's chart—acute vomiting	1.6	1.9	0.47
Patient diary—delayed vomiting	5.5	6.4	0.71

Outcomes measured by LASA score (mm) for nausea and vomiting and by number of vomiting episodes recorded in nurse's chart in the first 18 h and in patient diary over the next 7 days ($n = 70$).

Table 4. Control of emesis in first 18 h in 66 patients given both STADMAX and SAD

Control of emesis	No. of treatments STADMAX	SAD
Complete (no episodes)	30 (45%)	10 (15%)
Nearly complete (1–2 episodes)	26 (39%)	25 (38%)
Partial (3–5 episodes)	9 (14%)	18 (27%)
None (> 5 episodes)	1 (2%)	13 (20%)

$P < 0.0001$.

nausea or vomiting were noted on the basis of sex or age. In parallel group comparisons of the antiemetic treatments, SAD versus STADMAX, there was significantly less vomiting associated with STADMAX recorded on the nurse's chart ($P = 0.0001$). For other outcomes there was only sufficient power to detect differences between the two antiemetic treatments using crossover comparisons (below).

Cross over comparisons. Antiemetic control of two treatments during the acute phase based on the nurse's chart is summarised in Table 4 and Fig. 2. During the first 18 h significantly fewer episodes of vomiting were seen with STADMAX ($P < 0.0001$) with complete control achieved in 30/66 patients (45%) on STADMAX compared with 10/66 (15%) on SAD. Overall major control (≤ 2 vomiting episodes) was also significantly better with STADMAX (66 vs. 35; 85% vs. 53%) during this period. Only 1 patient (2%) on STADMAX had more than five episodes compared with 13 (20%) on SAD. Vomiting was most frequent 2–4 h after cis-DDP for both antiemetic regimens, occurring in 43 (65%) receiving SAD and 25 (38%) receiving STADMAX (Fig. 2).

Vomiting episodes over the next 7 days were also significantly less with STADMAX than SAD when based on the patient diary ($P = 0.03$) with total control achieved in 18/65 (28%) on STADMAX compared with 13/65 (20%) on SAD during this phase (Table 5). However, no significant differences were noted in patient perceptions of nausea, vomiting or appetite when based on patient-completed LASA scales.

Antiemetic side effects

The LASA scales measuring possible side effects of antiemetic treatments are summarised in Table 6. Two extra questions in

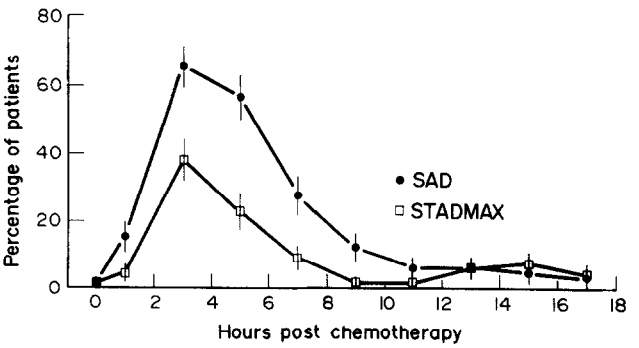

Fig. 2. Comparison of vomiting during the acute phase: SAD versus STADMAX. Average percentage of patients (mean ± standard error) with at least one vomiting episode in each 2 h period (0–2, 2–4, 4–6, 6–8, etc.) plotted against midpoint of each interval since starting chemotherapy.

Table 5. Patient assessment of nausea and vomiting for two antiemetic regimens: SAD vs. STADMAX

Item	No. of patients	Outcome SAD	Outcome STADMAX	*P*-value
LASA scales		Mean (mm)		
Nausea (after–before)	66	44	47	0.55
Vomiting (after–before)	66	42	38	0.37
Appetite	63	50	49	0.93
Recall	57	68	72	0.41
Patient diary (days 1–7)		Average Number		
Vomiting episodes	65	6.7	4.6	0.03
Antiemetic tablets	65	9.3	9.8	0.70
Days till eating normally	65	7.0	6.2	0.35

this section (the thought of an injection and the thought of staying in hospital) were used as possible surrogate measures for anticipatory nausea and vomiting. Patients receiving STADMAX had significantly more dry mouth ($P = 0.01$), blurred vision ($P = 0.03$) and diarrhoea ($P = 0.04$) while patients receiving SAD were significantly more restless ($P = 0.002$). Patients reported slightly more drowsiness with STADMAX though this was not statistically significant ($P = 0.11$). However, sedation scored by the nurse observer, was on average greater with STADMAX than SAD ($P = 0.02$). Significantly, no episodes of dystonic reactions were seen among patients on either regimen.

Patient preference

A primary outcome of the trial was the patient preference for either antiemetic treatment after two cycles. Of the 68 patients evaluated, 46 (68%) indicated they preferred STADMAX compared with 20 (29%) who chose SAD, while 2 (3%) had no preference ($P = 0.001$). The reasons for choosing STADMAX ($n = 46$) were: better control of nausea and vomiting in 31 (67%); fewer side effects in 12 (27%); no dehydration in 1; and no reason given in 2 patients. Preferences for SAD ($n = 20$) were due to: better antiemetic control in 7 (35%); early mobility in 6 (30%); fewer side effects in 6 (30%); while 1 patient experienced cisplatin induced renal failure after STADMAX and so chose SAD.

Table 6. Comparison of side effects for two antiemetic regimens: SAD vs. STADMAX

Item	No. of patients	SAD LASA scale Mean (mm)	STADMAX LASA scale Mean (mm)	*P*-value
Drowsiness	66	34	43	0.11
Restlessness	66	39	25	0.002
Confusion	66	15	16	0.79
Dry mouth	65	32	42	0.01
Blurred vision	66	10	18	0.03
Diarrhoea	66	7	13	0.04
Thought of injection	66	23	21	0.71
Thought of hospital	64	26	22	0.22

Period and carry-over effects

In view of the cross-over design treatment effects may be potentially confounded by changes in outcome over time (period effects) or changes in outcome due to the order of treatments (treatment-period interaction or carry-over effects). No period effects were found for any of the outcome measures. Tests for carry-over effects found no overall significant effects apart from the possibility of the "Thought of Staying in Hospital" ($P = 0.04$). As this was only one of 17 multiple comparisons for interactions, this is most likely due to chance.

DISCUSSION

The results of this study show the intensive multiagent regimen STADMAX is more effective than our previous best standard SAD in the control of both acute and delayed vomiting after cis-DDP chemotherapy. The explanation for improved efficacy may relate to one of several factors, since STADMAX used both more agents and, for some, at higher doses. The superiority of STADMAX may be due to its broader neurotransmitter blockade, particularly the impact of high dose metoclopramide on serotonin 3 receptors. The contribution of antihistamines [18] and anticholinergics [15] in preventing cisplatin emesis may be modest, however their role as a component of a multiple blockade model is little studied and could be more important. It is also possible that a dose response effect explains these results, with the use of high dose metoclopramide commenced prior to cis-DDP therapy and also a higher dose of dexamethasone used in the STADMAX regimen. High-dose metoclopramide may exert enhanced dopamine antagonism compared to that of serenace (haloperidol) and low dose metoclopramide used in the SAD regimen. It is not clear however, whether the increased efficacy of high dose metoclopramide is largely due to its dose dependent serotonin 3 antagonism or to enhanced dopamine antagonism, both of which are actions of this antiemetic.

The rationale for this antiemetic regimen without a specific serotonin 3 antagonist was primarily based on the lack of availability of such agents for clinical use in Australia both at the planning and execution stages of the study. The regimen gave the opportunity to investigate the feasibility of using several agents to block emesis at multiple sites in the pathway. We postulated that this intensive multiagent regimen would provide our new best standard treatment which would be suitable to test with the serotonin 3 antagonists when they became available.

Ondansetron, one serotonin 3 antagonist, has shown enhanced activity compared to high dose metoclopramide [19, 20], with major control of vomiting achieved in 72–75% vs. 41–42% of patients. However, single-agent ondansetron still only achieves total control of cis-platin induced emesis in 46–56% of patients [19, 20]. Thus this trial provides a suitable foundation on which to build future combination regimens in a similar way to which STADMAX was designed. For example, it has been shown already that dexamethasone can improve the effectiveness of ondansetron treatment when the two drugs are used in combination [21–23].

Comparison with other studies of emetic control should be made with caution due to differences in methodology and patient characteristics. Our trial, for example, did not include dry retching in the number of vomiting episodes. Nevertheless, the complete control in 45% and major control (≤ 2 episodes) in 85% of patients with STADMAX compares favourably with single agent ondansetron where complete control in 46–64% [19–21] and major control in 72–75% [19, 20] has been observed.

For ondansetron plus dexamethasone reported results have ranged from a major control rate of 78% [22] to a high complete control rate of 91% [21].

In our study, whilst the main benefit in antiemetic control from STADMAX was seen in the acute phase, less vomiting was also seen in the subsequent week as compared with SAD. This may be due either to the better initial control or to a prolonged scopolamine effect from the 3 day patch. The advantage of STADMAX over SAD was seen both for patients having at least 100 mg/m^2 of cisplatin and with regimens of lower doses of cisplatin. Subjective perceptions of nausea and vomiting based on LASA scales, however, were not significantly different. This may reflect either that the distress associated with nausea and vomiting is helped less than the physical episodes of vomiting or indicate a lack of discrimination of this LASA instrument for measuring nausea and vomiting. The latter explanation appears more likely due to the low reliability coefficient of LASA-rated nausea and vomiting and a clear preference for STADMAX expressed by most patients.

As anticipated more anticholinergic side effects were associated with STADMAX. There was significantly more akathisia associated with SAD. Importantly no dystonic reactions were seen in either group despite using high dose metoclopramide where this has occurred in 3–8% of patients in other series [18, 19]. The reduced akathisia and dystonia with STADMAX may be due to a protective effect of scopolamine [15] or the antihistamine clemastine [18].

The study design employed partial blinding of patients by means of a placebo patch to match the scopolamine transdermal patch. Patients were unaware which they received and to avoid any reporting bias, questioning of patients regarding possible anticholinergic effects was indirect and identical for both groups. Since nursing staff were aware of the antiemetic regimen used, the nurses chart could be subject to some observer bias, however with an objective measure like the number of vomiting episodes this is unlikely. For this reason, dry retching was excluded from the outcome measure of emesis as being too subjective and prone to observer bias. Nevertheless, dry retching was observed infrequently in either group.

In conclusion, we have demonstrated the efficacy of an intensive multiagent antiemetic regimen for platinum based chemotherapy. The regimen, based on multiple neurotransmitter blockade, provides a standard treatment where selective serotonin 3 antagonists are not available but also a model for improving on the single agent activity of this new class of drugs. Future trials of antiemetic treatments should consider similar strategies with outcome assessment including patient acceptability and costs of treatment.

1. Laslo J, Lucas VS. Emesis as a critical problem in chemotherapy. *N Engl J Med* 1981, **305**, 948–999.
2. Kearsley JH, Tattersall MHN. Recent advances in the prevention or reduction of cytotoxic-induced emesis. *Med J Aust* 1985, **143**, 341–346.
3. Coates, A, Abraham S, Kaye SB, *et al.* On the receiving end—patient perception of the side effects of cancer chemotherapy. *Eur J Cancer Clin Oncol* 1983, **19**, 203–208.
4. Gralla RJ, Itri LM, Pisko SE, *et al.* Anti-emetic efficacy of high-dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. *N Engl J Med* 1981, **305**, 905–909.
5. Cunningham D, Hawthorn J, Pople A, *et al.* Prevention of emesis in patients receiving cytotoxic drugs by GR 38 032 F a selective 5 HT3 Receptor antagonist. *Lancet* 1987, 1461–1452.
6. Kris MG, Gralla RJ, Clark RA, *et al.* Dose ranging evaluation of the serotonin antagonist GR C507/75 (GR 380 32F) when used as an antiemetic in patients receiving anticancer chemotherapy. *J Clin Oncol* 1988, **6**, 659–662.
7. Plezia PM, Alberts DS, Kessler J, *et al.* Immediate termination of intractable vomiting induced by cisplatin combination chemotherapy using an intensive five-drug antiemetic regimen. *Cancer Treat Rep* 1984, **68**, 1493–1495.
8. Borison HL, Wang SC. Physiology and pharmacology of vomiting. *Pharmacol Rev* 1953, **5**, 193–230.
9. Borison HL, McCarthy LE. Neuropharmocology of chemotherapy induced emesis. *Drugs* 1983, **25** (Suppl 1), 8–17.
10. Peroutka SJ, Snyder SH. Antiemetics: neurotransmitter receptor binding predicts therapeutic actions. *Lancet* 1982, **i**, 658–659.
11. Kilpatrick GJ, Jones BJ, Tyers MB. Identification and distribution of 5 HT3 receptors in rat brain using radioligand binding. *Nature* 1987, **330**, 746–748.
12. Fozard JT. Neuronal 5-HT receptors in the periphery. *Neuropharmacology* 1984, **23**, 1473–1486.
13. Friedlander MC, Kearsley JH, Sims K, *et al.* Lorazepam as an adjunct to anti-emetic therapy with haloperidol in patients receiving cytotoxic chemotherapy. *Aust NZ J Med* 1983, **13**, 53–56.
14. Kearsley JH, Diekman J, Sims K, *et al.* Single-agent versus combination anti-emetic treatment in patients receiving cytotoxic chemotherapy. *Med J Aust* 1982, **2**, 32–35.
15. Meyer BR, O'Mara V, Reidenberg MM. A controlled trial of the addition of transdermal scopolamine to a standard metoclopramide and dexamethasone antiemetic regimen. *J Clin Oncol* 1987, **5**, 1994–1997.
16. Hills M, Armitage P. The two-period cross-over clinical trial. *Br J Clin Pharmacol* 1979, **8**, 7–20.
17. McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika* 1947, **12**, 153–157.
18. Kris MG, Gralla RJ, Tyson LB, *et al.* Improved control of cisplatin induced emesis with high dose metoclopramide and with combinations of metoclopramide, dexamethasone and diphenolhydramine. Results of consecutive trials in 255 patients. *Cancer* 1985, **55**, 527–534.
19. Marty M, Pouillart P, Scholl S, *et al.* Comparison of the 5-hydroxytryptamine$_3$ (serotonin antagonist ondansetron) (GR38032F) with high dose metoclopramide in the control of cisplatin induced emesis. *N Engl J Med* 1990, **322**, 816–821.
20. De Mulder PHM, Seynaeve C, Vermorken JB, *et al.* Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. A multicentre, randomised, double-blind, crossover study. *Ann Intern Med* 1990, **113**, 834–840.
21. Tonato M. Ondansetron plus dexamethasone: an effective combination in high-dose cisplatin therapy. *Eur J Cancer* 1991, **27**, S12–S14.
22. Smith DB, Newlands ES, Rustin GJ, *et al.* Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containing chemotherapy. *Lancet* 1991, **338**, 487–490.
23. Cunningham D, Turner A, Hawthorn J, Rosin D. Ondansetron with and without dexamethasone to treat chemotherapy induced emesis. *Lancet* 1989, **i**, 1323–1324.

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