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The antiemetic efficacy of tropisetron plus dexamethasone as compared with conventional metoclopramide-dexamethasone combination in Orientals receiving cisplatin chemotherapy: a randomized crossover trial

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1 We report a single-blind randomized crossover trial comparing the efficacy of tropisetron plus dexamethasone (TROPDEX) *vs* conventional combination of metoclopramide, dexamethasone and diphenhydramine (METDEX) in prevention of acute and delayed vomiting in Chinese patients receiving high dose cisplatin.

2 Thirty-six consecutive patients with nasopharyngeal carcinoma were entered into the study, all received cisplatin at a dose range of 60–100 mg/m^2. Patients were randomized in the sequence of antiemetic regimens used in two consecutive cycles.

3 The TROPDEX regimen consisting of tropisetron 5 mg i.v. and dexamethasone 20 mg i.v. given on day 1 of chemotherapy, followed by oral maintenance with tropisetron 5 mg daily and dexamethasone 4 mg twice daily from day 2 to 6. The METDEX regimen consisting of metoclopramide 1 mg kg^{-1} i.v., dexamethasone 20 mg i.v. and diphenhydramine 25 mg i.v. given before chemotherapy and then 2 hourly for two more doses on day 1, followed by oral metoclopramide 20 mg 6 hourly from day 2 to 6.

4 Complete control of acute vomiting was observed in 64% of patients with TROPDEX as compared with 14% with METDEX ($P<0.01$). While complete plus major control of acute vomiting was observed in 84% with TROPDEX as compared with 58% with METDEX. The mean vomiting episodes on day 1 were 1.4 with TROPDEX as compared with 3.5 with METDEX ($P<0.01$). There was, however, no significant difference between the two regimens in the control of delayed vomiting.

5 When patients randomized to TROPDEX in the second cycle were compared with those with TROPDEX in the first cycle, the antiemetic efficacy was reduced, with mean acute vomiting episodes of 2 in the former compared with 0.8 in the latter ($P<0.01$).

6 The most common adverse effect observed was headache in TROPDEX (27%) and dizziness in METDEX (40%).

7 In conclusion, the antiemetic regimen TROPDEX is effective in Chinese patients receiving high dose cisplatin chemotherapy and is well tolerated. It is better than conventional METDEX regimen in the control of acute vomiting, but not in the control of delayed vomiting.

Keywords antiemesis cisplatin tropisetron dexamethasone metoclopramide Chinese

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Introduction

Patients receiving chemotherapy generally consider nausea and vomiting as the most feared side effect. Cisplatin, which is active against a wide range of tumours and being curative in some, is one of the highly emetogenic chemotherapeutic agents. Because of this, cisplatin has been regarded as the ideal drug for studying the efficacy of antiemetic regimens. Traditional methods of prophylaxis against cisplatin-induced emesis include high dose metoclopramide, anxiolytics, steroids, and combinations of the above [1–3]. The combination of high dose metoclopramide and dexamethasone, in particular, is effective against cisplatin-induced emesis with major control of emesis in 40–60% of patients. Unfortunately this regimen also leads to high incidence of extrapyramidal syndrome and acute dystonia reaction in 3–19% of patients, particularly in the younger age group. 5-HT_3 receptor antagonists were introduced several years ago as a new class of antiemetic agents. Clinical trials have confirmed the efficacy and good tolerability of these agents as a group. The commercially available preparations include ondansetron, granisetron and tropisetron. These agents differ mainly in their half-lives, receptor affinity and possibly mode of actions [4].

Tropisetron, one of the newer 5-HT_3 receptor antagonists, selectively blocks the excitation of presynaptic 5-HT_3 receptors of the peripheral nerves involved in the emetic reflex, and may have other direct actions in the central nervous system on 5-HT_3 receptors mediating the actions of vagal inputs to the area postrema [5]. Tropisetron metabolism is linked to the cytochrome P-450 2D6 isoenzyme system, which determines the polymorphism of debrisoquine/sparteine metabolism. There are phenotypical populations of extensive and poor metabolizers, and efficacy of tropisetron as well as tolerability may differ between the two groups.

In one study, no difference was observed between tropisetron and high dose metoclopramide cocktail in the control of acute and delayed vomiting induced by cisplatin-based chemotherapy, and the authors concluded that tropisetron is preferred because of better tolerability and ease of administration [6]. Other clinical studies showed that adding dexamethasone to tropisetron resulted in superior control of emesis than tropisetron alone [7–9]. Thus it seems that the combination of tropisetron and dexamethasone is better tolerated and at least as effective, if not better, than the high dose metoclopramide regimen (2 mg kg^{-1} $dose^{-1}$) commonly used.

The conventional antiemetic regimen used at our hospital follows the Stanford regimen which combined high dose metoclopramide (1 mg $kg^{-1} \times 3$) and dexamethasone (20 mg × 3). Although the total dose of metoclopramide is lower in this regimen as compared with the standard high dose scheme in literature, it is better tolerated by our patients with low incidence of extrapyramidal syndrome. This is particularly important as many of our patients receiving cisplatin-based chemotherapy are suffering from nasopharyngeal carcinoma and are relatively young. In our experience control of vomiting can be achieved using this conventional regimen in 40–60% of patients receiving high dose cisplatin. When tropisetron became available in 1993, the once daily dose was attractive compared with another 5-HT_3 receptor antagonist ondansetron requiring two to three doses. The daily cost of tropisetron is lower than ondansetron, although still much higher than our conventional regimen. Nordic experience did not show superiority of tropisetron over high dose metoclopramide [6]. This has important implications when the costs of antiemetic regimens are being considered. We think it is important to compare two regimens with optimal dose and combination in order to balance the antiemetic efficacy and side effects. To us, the Stanford regimen represents the optimal high dose metoclopramide regimen with infrequent adverse reactions while acheiving significant antiemetic control. In addition, difference in drug metabolism polymorphism exists between Orientals and Caucasians. To the best of our knowledge, no previous study regarding tropisetron plus dexamethasone in the Chinese population has been reported in the English literature. In order to compare the efficacy of tropisetron plus dexamethasone with our conventional antiemetic regimen in the Chinese population, we carried out a single-blind randomized crossover trial comparing these two regimens in patients receiving high dose cisplatin-based (60 mg m^{-2} or above) chemotherapy.

Methods

This was a single-blind randomized balanced crossover trial. Patients with nasopharyngeal carcinoma who were chemotherapy naive and scheduled to receive cisplatin at a dose range of 60–100 mg m^{-2} were randomized to receive either tropisetron plus dexamethasone (TROPDEX) or combination of metoclopramide, dexamethasone and diphenhydramine (METDEX) in the first cycle. Patients then crossed over to receive the other antiemetic regimen in the second cycle. Those with concomitant brain or gastrointestinal diseases that may themselves lead to nausea and vomiting were excluded from the study. Informed consent was obtained prior to registration. From June 1993 to August 1994, 36 consecutive patients were recruited into this study.

Patients did not know whether they were taking the new or conventional antiemetic regimen, although the two were clearly different. The investigators and the nursing staff who evaluated the antiemetic efficacy, however, were aware of the regimen being used. Although the study is single-blind only, assessement bias should be small since self-assessment was carried out by patients.

Antiemetic regimen

The TROPDEX regimen consisting of tropisetron 5 mg i.v. and dexamethasone 20 mg i.v. given 15 min before chemotherapy on day 1, followed by oral tropisetron 5 mg once daily and dexamethasone 4 mg twice daily

from day 2 to day 6. The METDEX regimen consisting of metoclopramide 1 mg m^{-2} i.v., dexamethasone 20 mg i.v. and diphenhydramine 25 mg i.v., given 15 min before chemotherapy and then 2 hourly for two more doses on day 1, followed by oral metoclopramide 20 mg 6 hourly from day 2 to day 6.

Compliance

Compliance was ascertained during hospitalization (day 1 to 3), as medications were either administered by nurses or taken under supervision. Thereafter patients were asked to record in the diary the number of tablets taken. Compliance was considered good if the patient took the prescribed medication, and poor if either part or all of the medication was not taken.

Methods of assessment

Patients were asked to record in a diary the episodes of vomiting and any adverse effects for 6 days after chemotherapy. Patients were also assessed by nursing staff with regard to compliance and side effects during the first 3 days of treatment. In order to avoid assessor bias, the nursing staff did not record the vomiting episodes of patients, but reminded patients to fill in the diary. Patients were usually discharged on day 4, and were asked to return the diary 2 weeks later. Control of vomiting was classified into four categories based on the number of vomiting episodes over periods of 24 h: complete control when there was no vomiting, major control—one to two episodes of vomiting, minor control—three to five episodes of vomiting, and failure—more than five episodes of vomiting. Control of nausea was not assessed in this study. Rescue with other antiemetics including metoclopramide, lorazepam and ondansetron were allowed but would be regarded as treatment failure. Acute vomiting represents vomiting occurred within 24 h after commencement of chemotherapy, while delayed vomiting represents vomiting after first 24 h. The mean vomiting episodes were calculated and analysed with two-tailed paired *t*-test. The frequencies of different categories of emetic control in the two regimens were also compared and analysed with Pearson's chi square test.

Table 1 Patient characteristics

	Group 1 n = *18*	*Group 2* n = *18*
Age, median	54	48
(years) mean	51	48
Sex, male/female	17/1	17/1
Antiemetic regimen:		
Cycle 1	TROPDEX	METDEX
Cycle 2	METDEX	TROPDEX
Cisplatin dose (number of patients)		
60 mg m^{-2}	6	5
80 mg m^{-2}	4	1
100 mg m^{-2}	8	12
Mean cisplatin dose (mg m^{-2})	82	89
Other chemotherapeutic agents (number of patients)		
Epirubicin	6	5
Mitoxantrone	4	1
5-fluorouracil	8	12

Results

Table 1 shows the patient characteristics and chemotherapy regimens used. Group 1 represents patients randomized to receive TROPDEX in the first cycle and METDEX in next cycle, while group 2 patients had the reverse sequence. Although more patients in group 2 had higher cisplatin dose, this is not a major source of bias in a crossover study. Only two female patients were included in the study, the majority being male patients.

Compliance was good during hospitalization from day 1 to 3. However compliance decreased from day 4 to 6, especially during the last 2 days. There was no apparent difference between the two regimens with respect to patient compliance (Table 2).

Table 3 shows the mean episodes of vomiting with the two regimens in 6 consecutive days after chemotherapy. There were significantly less vomiting episodes with TROPDEX (1.4) as compared with METDEX (3.5) on day 1 ($P < 0.01$, paired *t*-test). No significant difference was observed in subsequent days.

A more useful way to analyse the result is to express the degree of emesis control in the 6 consecutive days

Table 2 Patient compliance

Days after starting chemotherapy	*TROPDEX* n = *36*			*METDEX* n = *36*		
	Good	*Poor*	*Unknown*	*Good*	*Poor*	*Unknown*
1	36	0	0	36	0	0
2	36	0	0	36	0	0
3	36	0	0	36	0	0
4	32	1	3	31	2	3
5	29	4	3	27	6	3
6	28	5	3	27	6	3

Table 3 Mean episodes of vomiting with the two regimens in 6 consecutive days after chemotherapy

Days after chemotherapy	*Mean episodes of vomiting* TROP/DEX	*Cocktail*	P *value*
1	1.4	3.5	<0.01
2	2.6	3.3	0.13
3	2.0	2.3	0.63
4	1.2	1.5	0.39
5	0.7	0.9	0.51
6	0.3	0.6	0.27

(Figure 1). Complete control of acute vomiting was observed in 64% (23 out of 36) of patients with TROPDEX, as compared with 14% (5 out of 36) of patients with METDEX ($P<0.01$, Figure 1a). Complete plus major control of acute vomiting (two episodes of vomiting or less) was observed in 84% of patients with TROPDEX as compared with 58% with METDEX. Failure to control acute vomiting was observed in 10% (4 out of 36) of patients with TROPDEX as compared with 17% (6 out of 36) with METDEX.

Complete control of vomiting decreased to 33% on day 2 and 39% on day 3 with TROPDEX, as compared with 28% on day 2 and 24% on day 3 with METDEX. Although complete control of vomiting on day 2 and 3 continued to be higher in patients receiving TROPDEX than METDEX, the difference was not statistically significant (Figure 1b and c). No significant difference was observed also in the control of vomiting from day 4 to 6. On day 5 and 6, no failure was observed in either group (Figure 1d–f).

Figure 2 shows the control rate of acute vomiting (complete plus major) for the two antiemetic regimens during each cycle of chemotherapy. While there was no apparent difference in antiemetic efficacy of METDEX whether administered in the first or second cycle, the efficacy of TROPDEX was reduced when administered during the second cycle (i.e. after the METDEX) as compared with the first one. 94% of patients randomized to receive TROPDEX in the first cycle achieved complete or major control of acute vomiting, as compared with 72% of patients randomized to the reverse sequence.

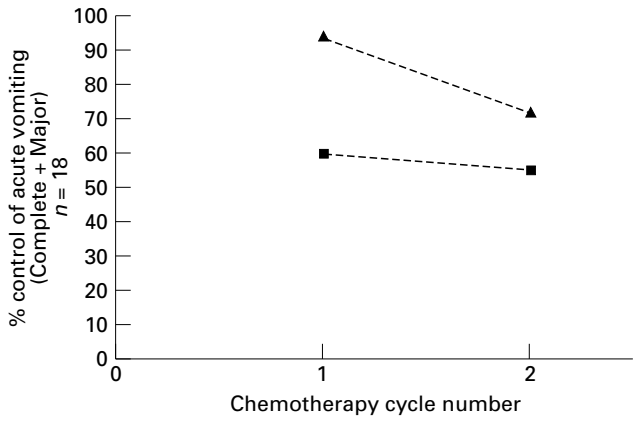

Figure 2 Control of acute vomiting with the two antiemetic regimens (▲ TROP/DEX; ■ MET/DEX) in chemotherapy cycle 1 and 2. The lines connecting the symbols are used to highlight the differences between two groups who received the antiemetic regimen specified either in cycle 1 or cycle 2.

Both regimens were well tolerated. The most common adverse effect was headache which occurred in 27% of patients receiving TROPDEX, and dizziness which occurred in 40% of patients receiving METDEX. No extrapyramidal syndrome or acute dystonia reaction was observed. The adverse effects were usually mild, and no patient needs to discontinue the medication because of adverse effects.

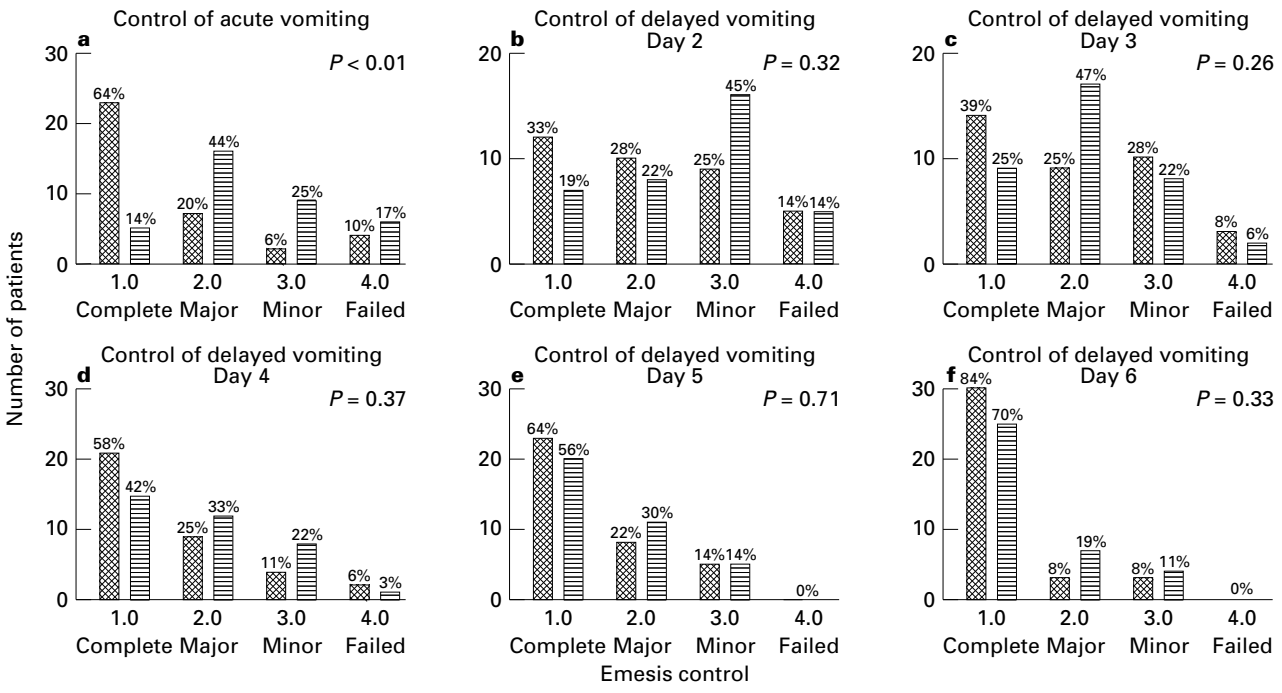

Figure 1a–f Control of vomiting with the two antiemetic regimens in six consecutive days after starting chemotherapy. ▨ TROP/DEX; ▤ MET/DEX.

Discussion

This study consisted mainly of male subjects, and the conclusion should be interpreted in the light of this, as gender could affect the emetic response. Our study confirms the effectiveness of the combination TROPDEX in controlling acute vomiting induced by high dose cisplatin-based chemotherapy. In the Nordic study [6] which consisted of 259 patients, no significant difference was observed in the complete control of acute vomiting between tropisetron and conventional metoclopramide–dexamethasone regimen. We did observe better control of acute vomiting with TROPDEX as compared with our conventional antiemetic regimen. This could be due to addition of dexamethasone to tropisetron with enhancement of antiemetic effect, and the fact that our conventional antiemetic regimen used a lower dose of metoclopramide in order to reduce extrapyramidal syndrome. However we did not find maintenance tropisetron, even with addition of dexamethasone, to be superior to metoclopramide alone in controlling delayed vomiting. In fact control of emesis was most difficult during second and third days of treatment, with complete control of vomiting achieved in 25 to 39% of patients only. Thus delayed emesis remains the major problem in patients receiving high dose cisplatin chemotherapy. The role of maintenance tropisetron in the control of delayed vomiting needs to be more carefully studied. Use of other 5-HT_3 receptor antagonists such as ondansetron as maintenance therapy also failed to improve control of delayed emesis induced by cisplatin [10]. The mechanism of delayed emesis is still unknown, although prior experience suggests that improving the control of acute emesis may reduce delayed emesis [11,12]. Kris *et al.* demonstrated in their randomized trial that oral metoclopramide plus dexamethasone was superior to either dexamethasone alone or placebo in controlling delayed emesis in patients treated with high dose cisplatin [13]. Further studies on the control of delayed emesis, as well as direct comparison of the different 5-HT_3 receptor antagonists are thus needed.

Currently, the optimal antiemetic regimen in terms of cost-effectiveness would be the use of 5-HT_3 receptor antagonist plus dexamethasone on day 1 of chemotherapy, followed by combination of metoclopramide, dexamethasone and anxiolytic in subsequent days. If indeed no difference exits between the different 5-HT_3 receptor antagonists, then the one with lowest cost should be used.

The observation of reduced efficacy of TROPDEX when administered after METDEX may due to two reasons. Firstly, some patients randomized to receive TROPDEX in the second cycle had higher cisplatin dose as compared with those who received TROPDEX in the first cycle. This may affect the degree of emesis and thereby the antiemetic control. Secondly, prior experience with poor emesis control is known to affect subsequent response to other antiemetic regimens (the carry-over effect), thus when TROPDEX was used after METDEX, the efficacy could be reduced. Although tropisetron plus dexamethasone is still effective in patients responding poorly to previous conventional antiemetic therapy [14], our finding suggests the early use of tropisetron and dexamethasone in order to achieve maximal effect.

In conclusion, combination of the 5-HT_3 receptor antagonist tropisetron and dexamethasone is highly effective as an antiemetic regimen in patients receiving high dose cisplatin-based chemotherapy. It is superior to the conventional metoclopramide-dexamethasone regimen in controlling acute vomiting. There is, however, no significant difference between maintenance tropisetron–dexamethasone and metoclopramide alone in the control of delayed vomiting. Apart from headache, tropisetron is well tolerated with minimal side effects.

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