Anti-emetic effect of high-dose metoclopramide vs alizapride – a randomised crossover study

KHOO TAN HOON SENG¹, CHUA EU TIONG¹ & TAN CHOR HIANG²

¹Department of Therapeutic Radiology, Singapore General Hospital and ²Planning Department, Ministry of Health, Singapore

A randomised double-blind crossover study was undertaken to compare the anti-emetic efficacy of alizapride against high dose metoclopramide. A total of 32 patients on cisplatin were randomised to receive either high dose metoclopramide (7 mg kg⁻¹ day⁻¹) or alizapride (5 mg kg⁻¹ day⁻¹). Anti-emetic responses in terms of control of vomiting episodes were similar in both regimens (59%). However, patients showed a statistically significant preference for high dose metoclopramide ($P = 0.02$). Side effects of both regimens were minimal. We conclude that alizapride is not superior to high dose metoclopramide in controlling cisplatin induced vomiting.

Keywords alizapride high dose metoclopramide cisplatin anti-emesis

Introduction

Emesis is probably the most distressing and unpleasant side-effect of chemotherapy [1]. Some patients chose to abandon their chemotherapy rather than face the repeated agony of emesis. High dose metoclopramide has been the most widely utilised anti-emetic agent for cisplatin chemotherapy. Several reports have shown significant control of emesis with this drug [2, 3]. In the Department of Therapeutic Radiology, Singapore General Hospital, we had adopted high dose metoclopramide as our standard anti-emetic regime for patients receiving cisplatin.

Alizapride is a new substituted benzamide, developed in Europe. Its formula is *N*-(allyl-1-pyrrolidinyl-2) methyl methoxy 6-1-H-benzotriazole carboxamine-5. Though similar in many of its properties to metoclopramide, it displayed a significantly greater anti-emetic effect than metoclopramide in experimental animals on apomorphine and dihydroergotamine [4]. A few early clinical trials have also suggested that alizapride was superior to metoclopramide. [4, 5].

In this study, we compared the anti-emetic efficacy of alizapride with high dose metoclopramide in patients receiving cisplatin and sought any differences in side effects of the two regimens.

Methods

From 1987 to 1989, all consecutive patients scheduled for cisplatin chemotherapy at a dose of 100 mg/m² were offered entry into this study. Informed consent was obtained and they were then randomised to receive either high dose metoclopramide or alizapride. Other entry criteria included age 70 years or less, no prior exposure to chemotherapy, and no gastrointestinal disorder.

Metoclopramide was administered at 7 mg kg⁻¹ as a 24 h continuous intravenous infusion, starting 0.5 h before the cisplatin delivery. Alizapride was given at the recommended dose of 5 mg kg⁻¹ day⁻¹ in divided intravenous doses at 4.5 hourly intervals. The first dose was given 0.5 h prior to cisplatin. Each dose of alizapride was diluted in 50 ml of normal saline and infused over 15 min.

For the second cycle of cisplatin, which was given 4 weeks later, the anti-emetic regime was switched so that patients receiving high dose metoclopramide in the first course would now get alizapride, and *vice-versa*. Following each cycle of chemotherapy, which was given on an in-patient basis, the patients reported the number of episodes of vomiting to an independent observer who was blind to the regimen given. Following the end of the second course, the patients

were asked to state which anti-emetic therapy was better, in terms of control of emesis. Any side effects were noted.

To grade the anti-emetic response, the following criterion was used: complete response meant no vomiting episodes, partial response implied 5 or fewer episodes, and no response was 6 or more episodes of vomiting. The non-parametric Fisher's exact test was used to compare differences between the two groups.

Results

A total of 36 patients were entered into the study. Their ages ranged from 20 to 69 years with a mean of 43.5 years for males and 47 for females. Four patients were excluded from the analysis because they failed to complete their scheduled two cycles of chemotherapy. Thirty-two patients were available for analysis, 16 of each sex.

A variety of cancers were treated, with a preponderance of ovarian, testicular and nasopharyngeal tumours, reflecting the established role of cisplatin in these conditions.

With high dose metoclopramide, 19 of 32 patients (59.4%) had their emesis controlled, i.e. complete and partial response. Four (12.5%) had no vomiting episodes. A similar proportion of patients, 19 of 32 (59.4%), also exhibited response to alizapride with five complete responders (15.6%). Hence there was no difference in responses between the two regimens (Table 1).

However more patients preferred high dose metoclopramide, 21 of 32 (65.6%) compared with 11 of 32 (34.4%) preferring alizapride (Table 2). This difference was statistically significant ($P = 0.02$).

There was no significant correlation between body weight or body surface area and response.

Side effects from either regimen were minimal, and were alleviated with simple measures. One patient had extrapyramidal symptoms on high dose metoclopramide and two had minor complaints of giddiness, drowsiness, and diarrhoea. One patient on alizapride had diarrhoea. Symptomatic hypotension, a reported side effect of alizapride [6, 7, 8], was not seen in our patients.

Discussion

Our study showed that the response rate of control of emesis was similar in both regimens (59%), based on objective assessment of the actual number of vomiting episodes, a method used in other anti-emetic studies [6, 9, 10].

Nausea is a difficult phenomenon to quantify. Many patients may have long periods of nausea without actual vomiting and this can be just as debilitating as vomiting itself. In an effort to encompass this effect in our assessment, we requested patients to indicate which anti-emetic regime they preferred. Analysis showed that a significant number preferred high dose metoclopramide.

In this study, high dose metoclopramide was taken as the standard regimen with which to compare alizapride, because it has been widely accepted at that time as the best for cisplatin induced vomiting [11, 12]. Alizapride was given at the recommended dose of 5 mg kg⁻¹ day⁻¹. Higher doses have been reported to cause hypertension, arrhythmia and diarrhoea without increasing its anti-emetic efficacy.

The response rate of high dose metoclopramide of 59% was comparable with other studies using such doses [3, 12]. Alizapride gave the same response rates (59%), higher than a previously reported randomised study (34%) [7]. A high response was found in an earlier study [10].

Table 1 Response to anti-emetics

Vomiting episodes	With high dose metoclopramide			With alizapride		
	Male	Female	Total	Male	Female	Total
0	2	2	4 (12.5%)	3	2	5 (15.6%)
1-5	6	9	15 (46.9%)	5	9	14 (43.8%)
6 or more	8	5	13 (40.6%)	8	5	13 (40.6%)
Total	16	16	32 (100%)	16	16	32 (100%)

Table 2 Patient's preference

Patient's choice	Order of anti-emetic administration		Total
	Alizapride – high dose metoclopramide	High dose metoclopramide – alizapride	
Alizapride	3	8	11 (34.4%)
Metoclopramide	15	6	21 (65.6%)
Total	18	14	32 (100.0%)

Fisher's test, $P = 0.02$.

Side effects were uncommon and mild in both regimens. Only one patient had extrapyramidal symptoms, which were controlled with parenteral diazepam.

Prior exposure to chemotherapy did not appear to prejudice the patients to subsequent cycles, as in both sequences of cross-over, the second anti-emetic regimen, regardless of it being high dose metoclopramide or alizapride, was preferred. This was unexpected as we predicted that anticipatory vomiting would have produced a reverse effect to that observed.

In conclusion, we found that alizapride did not prove to be superior to high dose metoclopramide in controlling cisplatin induced emesis, and patients preferred the latter regimen.

The authors would like to thank the following in the Department of Therapeutic Radiology, Singapore General Hospital, for including their patients into the study: Dr E. J. Chua, H. Khor, Dr B. C. Tan, Dr Florence Lim.

References

- Coastes A, Abraham S, Kaye SB, *et al.* On the receiving end: patients' perception of the side effects of cancer chemotherapy. *Eur J Cancer* 1983; **19**: 203–208.
- Cunningham D, Soukop M, Gilchrist NL, *et al.* Randomised trial of intravenous high metoclopramide and intramuscular chlorpromazine in controlling nausea and vomiting induced by cytotoxic drugs. *Br med J* 1985; **290**: 604–605.
- Gralla RJ, Itri LM, Pisko SE, *et al.* Antiemetic efficacy of high metoclopramide: randomised trials with placebo and prochlorperazine in patients with chemotherapy induced nausea and vomiting. *New Engl J Med* 1981; **305**: 905–909.
- Perrot J, Nahos GJ, Lanille C, Debay A. *Substituted benzamides as antiemetics in treatment of cancer chemotherapy induced nausea and vomiting*, Masson Publishing, New York, Masson Publishing USA Inc., 1981: 195–202.
- Cupiso D, Favier F, Favier C. Evaluation d'un nouvel anti-emetique, 1 alizapride, en cancerologie. *Sem Hos Paris* 1982; **58**: 1370–1373.
- Saller R, Hellenbrecht D. Comparison of the antiemetic efficacy of two high dose benzamides, metoclopramide and Alizapride against cis-platinum induced emesis. *Cancer Treat Rep* 1985; **69**: 1301–1303.
- Joss RA, Galeazzi RL. The anti-emetic activity of high dose alizapride and HD MCP in patients receiving cancer chemotherapy: A prospective double-blind trial. *Clin Pharmac Ther* 1986; **39**: 619–624.
- Bleiberg H, Rozenzweig M, Nicaise C. High dose alizapride: Phase I study in cancer patients receiving cis-platinum (Abstract) Brussels, *Proceedings of the Fourth NCI-EORTC Symposium in new drugs in cancer therapy*. Dec 14–17 1983.
- Parikh PM, Charak BS. A prospective randomized double-blind trial comparing metoclopramide alone with metoclopramide plus dexamethasone in preventing emesis induced by high dose cis-platinum. *Cancer* 1988; **62**: 2263–2266.
- Clavel M, Pommatau E. Alizapride and chemotherapy: A report of 8 years experience (Abstract). Brussels. *Proceedings of the Fourth NCI-EORTC Symposium in new drugs in cancer therapy*. Dec 12–14 1983.
- Kearsley JH, Tattersall MHN. Prevention of cytotoxic induced nausea and vomiting. *Recent advances in clinical oncology*. Second Edition. Churchill Livingstone 1986: 222–235.
- Warrington PS. Optimising anti-emesis in cancer chemotherapy-efficacy if continuous versus intermittent infusion of high dose metoclopramide in emesis induced by cis-platinum. *Br med J* 1985; **293**: 1334–1337.

(Received 1 November 1993,
accepted 12 May 1994)