Ondansetron versus Metoclopramide, both Combined with Dexamethasone, in Prevention of Emesis induced by Chemotherapy

[1] Bahir Abdul Razzaq Mshimesh , [2] Munoor Abdul Ilah Al Nakash

and[3] Dalia Abd Al-Kader Al Salihy

[1,3] Department of Pharmacotherapy -College of Pharmacy /AL- Mustansiriya University
[2] Department of Oncology - Baghdad Teaching Hospital.

Abstract

Background:

Prophylactic use of 5-hydroxytryptamine$_3$ receptor antagonists after the first 24 h of exposure to emetic chemotherapy (to decrease the incidence of delayed phase emesis) cause an increase in the cost of treatment.

Objective:

We designed a study to evaluate the efficacy of a setron (ondansetron) in the acute and delayed phase, compared with metoclopramide, each combined with a corticosteroid.

Patients and methods:

On their course of single day emetic chemotherapy (cisplatin, carboplatin, doxorubicin, cyclophosphamide and others), one hundred patients completed this study and were divided into two groups: first group involves 52 patients received ondansetron 8 mg i.v. + dexamethasone 8 mg i.v. on day 1 as pre-chemotherapy, followed for 5 days by ondansetron 8 mg tid orally + dexamethasone 4 mg bid orally; second group involves 48 patients received metoclopramide 10 mg i.v. + dexamethasone 8 mg i.v. on day 1 as pre-chemotherapy, followed for 5 days by metoclopramide 10 mg tid orally + dexamethasone 4 mg bid orally. Patients evaluated the results using a diary card.

Results:

Control of acute emesis in both arms was similar (86% for ondansetron gr. and 85% for metoclopramide gr.). These well controlled patients also had control of delayed emesis in 81% of ondansetron and 84% of metoclopramide treated cases. Patients experiencing acute emesis had poor control in the delayed phase. Incidence of toxicity was variable between the two arms.

Conclusion:

Administration of i.v. ondansetron with dexamethasone achieves an extremely high control of acute emesis. Our data suggest that routine prescription of setrons for delayed phase control is not advisable as it increases the cost without any benefit over metoclopramide for the majority of patients. Delayed emesis in the rare patients with acute phase emesis remains an unsolved problem.

Key words: Acute emesis, delayed emesis, dexamethasone, ondansetron, metoclopramide.

مقارنة خليط ال dexamethsone+ ondansetron مع خليط ال dexamethsone + metoclopramide في الحد من الغثيان والتقيؤ المرتبط بالعلاج الكيمياوي

الخلاصة

معروف ان الاستعمال الوقائي لادوية مضادات القيء (setrons) المصاحب للعلاج الكيمياوي يرفع من الكلفة العلاجية لمرضى السرطان . لذلك صممت هذه الدراسة لتقييم فاعلية هذه الادوية ، مقارنة بدواء الـ metoclopramide ،وبوجود الـ dexamethasone في الحد من هذه التأثيرات الجانبية .

شملت هذه الدراسة (100) مريض قسموا الى مجموعتين : الأولى (52 مريض) : استلم المرضى حقن وريدية من (ondansetron 8mg + dexamethsone 8mg) نصف ساعة قبل اعطاء العلاج الكيمياوي في اليوم الاول. في الايام الخمسة التالية استلموا فمويا الـ ondansetron 8mg ثلاث مرات في اليوم مع الـ dexamethsone 4mg مرتان في اليوم. الثانية (48 مريض) : استلم المرضى حقن وريدية من(metoclopramide10mg + dexamethsone 8mg) نصف ساعة قبل اعطاء العلاج الكيمياوي في اليوم الاول. في الايام الخمسة التالية استلموا فمويا الـ metoclopramide10mg ثلاث مرات في اليوم مع الـdexamethsone 4mg مرتان في اليوم.

بينت النتائج ان نسب السيطرة على الطور المبكر (اليوم الاول) من التقيؤ كانت 86% لمجموعة الـ ondansetron و85%لمجموعة الـmetoclopramide .اما نسب السيطرة على الطور المتأخر (2-6 يوم) فكانت 81%و 84% على التوالي للمجموعتين العلاجيتين . اما المرضى الذين لم يتم السيطرة على تقيؤهم الحاد في الطور المبكر فقد استمر عندهم الغثيان والتقيؤ في الطور المتأخر .بالنسبة للاثار الجانبية لهذه الادوية فقد تفاوتت نسب حدوثها بين المجموعتين العلاجيتين .

في ضوء هذه النتائج يمكننا الاستنتاج بأن خليط الـ ondansetron + dexamethsone له قابلية عالية في السيطرة على الطور المبكر للتقيؤ في حين ان سيطرته على الطور المتأخر كانت اقل فاعلية من خليط الـ dexamethsone + metoclopramide اضافة الى كلفته العلاجية العالية لذلك لاننصح باستعماله في الطور المتأخر من الغثيان والقيء.

مفاتيح البحث : التقيؤ الحاد – التقيؤ المتأخر- dexamethsone- ondansetron -metoclopramide .

Introduction

Nausea and vomiting are the most distressing side effects of cytotoxic chemotherapy. Metoclopramide giving its antiemetic effect by blocking dopamine$_2$-receptors centrally and peripherally. The prophylactic use of 5-hydroxytryptamine$_3$-receptor antagonist (setron) in combination with corticosteroid is the recommended standard for prevention of acute emesis caused by moderately to highly emetic chemotherapy [1,2,3]. However, the administration of highly and moderately emetic cytotoxic agents causes nausea and vomiting not only within 24 h after the start of chemotherapy (acute emesis), but also during the following days (delayed emesis). The pathophysiology of delayed emesis in contrast to that of acute emesis is largely undefined. Setrons are not universally accepted as a standard in preventative treatment of delayed emesis, in spite of some positive studies [1]. This might be due to methodological problems, as many studies did not take acute emesis into account as a predictive factor for delayed emesis.

We designed this study to evaluate the efficacy and safety of ondansetron in the acute and delayed emesis phase, compared with metoclopramide, both agents being combined with a corticosteroid.

Patients and methods

This randomized clinical trial was carried out on patients receiving their course of moderately or highly emetic single day chemotherapy, at Baghdad Teaching Hospital/Department of Surgery/Unit of Oncology, under follow up of specialist doctors during the period from January to June 2010.

Patients were excluded if any of the following applied: severe concurrent illness, vomiting due to some other cause, antiemetic therapy administered
concurrently or in the 24 h preceding chemotherapy, administration of benzodiazepines, vomiting in the 24 h before chemotherapy, concurrent radiation therapy, impaired renal function (serum creatinine >2.0 mg/dl), jaundice (serum bilirubin >2.0 mg/dl) or an elevated aminotransferase level (SGOT/SGPT > twice the upper normal limit).

From 109, only 100 patients completed this study (as others were excluded due to poor compliance with the follow up program) and were divided into two groups: first group involves 52 patients received ondansetron 8 mg i.v. + dexamethasone 8 mg i.v. 30 minutes before chemotherapy on day 1; second group involves 48 patients received metoclopramide 10 mg i.v. + dexamethasone 8 mg i.v. 30 minutes before chemotherapy on day 1. Then both groups were treated with a moderately to highly emetic chemotherapy regimen containing cisplatin ≥50 mg/m^2, carboplatin ≥300 mg/m^2, dacarbazine ≥500 mg/m^2, doxorubicin ≥40 mg/m^2, ifosfamide ≥1200 mg/m^2, or cyclophosphamide ≥600 mg/m^2. After the acute phase therapy, the next morning was used as the time point to begin treatment against possible delayed emesis where: first group received ondansetron 8 mg tid orally + dexamethasone 4 mg bid orally on days 2–6; second group received metoclopramide 10 mg tid orally + dexamethasone 4 mg bid orally on days 2–6. With the help of the medical team, patients instructed to fill the diary card on which they had to indicate daily (for days 1–6) whether they experienced any nausea or vomiting or other side effects [4]. On the next clinical visit, patients give the completed diary card to the Unit of Oncology.

The main endpoint of this trial was control of emesis, defined as only mild nausea (not interfering with normal daily life) and no vomiting over the period of 5 days after emetic chemotherapy. The primary evaluation of this main endpoint was related to the group of patients with control of acute emesis (for 18–24 h after treatment). Randomization was stratified by sex; chemotherapy naïve versus previous chemotherapy; smoking; and chemo-therapy regimen (cisplatin or carboplatin versus others).

Statistical analysis

The trial was planned to have a size that would be sufficient to detect any significant difference in the rates of control between the two arms of the study [5,6]. Data were expressed as proportions (number or percentage of patients) and the chi-square test was used for statistical evaluation of significant difference between both therapeutic groups. *P*-value of < 0.5 was regarded as significant.

Results

The distribution of parameters for stratification at randomization is shown in Table (1). Despite the exclusion of nine patients who had no data about delayed emesis, the stratification parameters were well balanced (no statistically significant difference, P >0.05) between the two treatment arms. Other patient characteristics are shown in Table (2).

Table (1): Stratification factors.

Parameters	Ondan+dexa (n = 52)	Meto+dexa (n = 48)
Sex		
Male	22(42%)	20(42%)
Female	30(58%)	28(58%)
Chemotherapy		
Naïve	45(86.5%)	42(87.5%)
Previous	7(13.5%)	6(12.5%)
Smoking		
Yes	12(23%)	11(23%)
No	40(77%)	37(77%)
Chemotherapy regimen		

Cisplatin	18(34%)	16(33%)
Carboplatin	17(33%)	15(32%)
Others	17(33%)	17(35%)

No statistically significant differences (p>0.05).

Table (2): Patient characteristics at randomization.

Characteristics	Ondan+dexa (n = 52)	Meto+dexa (n = 48)
Age (years)		
Median	55	56
Range	23–85	20–88
Tumor surgery		
Yes	3(6%)	2(4%)
No	49(94%)	46(96%)
Site of tumor		
Breast	13(25%)	12(25%)
Lung	11(21%)	10(21%)
Gastric	10(19%)	9(19%)
Cervix	8(15%)	8(16%)
Head and neck	6(12%)	5(11%)
Other sites	4(8%)	4(8%)

No statistically significant differences (p>0.05).

Table (3) shows the rate of acute emesis on day 1, as reported by the patients on the diary card. The low rate of acute emesis (14% severe nausea or vomiting) obtained with setron and corticosteroid combination confirming the high degree of protection from this phase and was comparable to that obtained with metoclopramide and corticosteroid combination (15% severe nausea or vomiting).

Table (3): Acute emesis control .

Acute emesis	Ondan+dexa (*n* = 52)	Meto+dexa (*n* = 48)	Total (*n* = 100)
None	35 (67%)	33(68%)	68 (68%)
Mild nausea, no vomiting	10 (19%)	8 (17%)	18 (18%)
Severe nausea, no vomiting	2 (4%)	2 (4%)	4 (4%)
Vomiting with or without nausea	5 (10%)	5 (11%)	10 (10%)

No statistically significant differences ($p>0.05$).

There was no significant difference ($p>0.05$) in the control of acute emesis between the two treatment arms. Thus, the results of the delayed phase are not influenced by a difference in control during the acute phase, which may have been the case as patients with acute emesis are much more likely to experience delayed emesis. A more detailed analysis shows that acute emesis was lower under carboplatin than cisplatin or any other chemotherapeutic agents (Table 4).

Table (4): Acute emesis by chemotherapeutic agents .

Chemotherapeutic agent	Ondan+dexa	Meto+dexa	Total
Cisplatin	*n* = 18	*n* = 16	*n* = 34
None	11 (63%)	10 (64%)	21 (64%)
Mild nausea, no vomiting	3 (16%)	2 (13%)	5 (15%)
Severe nausea, no vomiting	1 (5%)	1 (6%)	2 (5%)
Vomiting with or without nausea	3 (16%)	3 (17%)	6 (16%)
Carboplatin	*n* =17	*n* = 15	*n* = 32
None	14 (85%)	13 (84%)	27 (84%)
Mild nausea, no vomiting	3 (15%)	2 (16%)	5 (16%)
Severe nausea, no vomiting	0	0	0
Vomiting with or without nausea	0	0	0
Other agents	*n* = 17	*n* = 17	*n* = 34
None	10 (57%)	10 (59%)	20 (58%)
Mild nausea, no vomiting	4 (24%)	5 (29)	9 (27%)

Severe nausea, no vomiting	1 (6%)	1 (6%)	2 (5%)
Vomiting with or without nausea	2(13%)	1(6%)	3 (10%)

No statistically significant differences (p>0.05).

Control of delayed emesis (equivalent to the mild nausea and no vomiting) on days 2–6 is shown in Table (5). The rate of delayed emesis obtained with setron and corticosteroid combination was 19% (severe nausea or vomiting) and for metoclopramide and corticosteroid combination was 16% (severe nausea or vomiting).

Table (5): Delayed emesis control .

Delayed emesis	Ondan+dexa (n = 52)	Meto+dexa (n = 48)	Total (n = 100)
None	30 (56%)	26 (54%)	56 (56%)
Mild nausea, no vomiting	13 (25%)	14 (30%)	27 (27%)
Severe nausea, no vomiting	5 (10%)	4 (8%)	9 (9%)
Vomiting with or without nausea	4 (9%)	4 (8%)	8 (8%)

No statistically significant differences (p>0.05).

A more detailed analysis for control of delayed emesis according to the three categories of emetic chemotherapy is shown in Table (6). Control of delayed emesis is very similar (no statistically significant difference, P >0.05) between the two treatment arms. The total rate of control was 62.5% under cisplatin, 81.5% under carboplatin, and 82% under other chemo-therapeutic agents.

Table (6): Delayed emesis by chemotherapeutic agents .

Chemotherapeutic agent	Ondan+dexa	Meto+dexa	Total
Cisplatin	n = 18	n = 16	n = 34
None	7 (38%)	6 (37%)	13 (37.5%)
Mild nausea, no vomiting	4 (24%)	4 (26%)	8 (25%)
Severe nausea, no vomiting	1(5%)	1 (6%)	2 (5.5%)
Vomiting with or without nausea	6 (33%)	5(31%)	11 (32%)
Carboplatin	n = 17	n = 15	n = 32
None	10 (60%)	8 (53%)	18 (56.5%)
Mild nausea, no vomiting	4 (23%)	4 (27%)	8 (25%)
Severe nausea, no vomiting	2 (12%)	2 (14%)	4(13%)
Vomiting with or without nausea	1(5%)	1 (6%)	2 (5.5%)
Other agents	n = 17	n = 17	n = 34
None	8 (47%)	7 (41%)	15 (44%)
Mild nausea, no vomiting	6 (35%)	7 (41%)	13 (38%)
Severe nausea, no vomiting	2(12%)	2 (12%)	4 (12%)
Vomiting with or without nausea	1 (6%)	1 (6%)	2 (6%)

No statistically significant differences ($p>0.05$).

The primary endpoint was control of emesis during the delayed phase in patients having control during the acute phase. This clinical trial does not show any statistically significant difference ($p>0.05$) between the treatment arms. The confidence intervals for nausea and vomiting control in the two treatment arms overlap to a large extent during acute and delayed emesis (table 7).

Table (7): Comparsion between treatment groups *p*-values.

Patient category	Ondan+dexa (n = 52)	Meto+dexa (n = 48)	Chi-square
Acute emesis control (day 1)	45 (86%)	41 (85%)	P >0.05
95% confidence interval	79% to 93%	78% to 92%	
Delayed emesis control (days 2–6)	43 (81%)	40 (84%)	P >0.05
95% confidence interval	74% to 88%	77% to 91%	

During antiemetic treatment, toxicities other than nausea or vomiting were reported on the diary card by the patients and on a predesigned form filled in by the investigator team at the next visit to

the hospital; these are summarized in Table (8). It can be observed that more patients reported abnormal movements on the setron (we have expected that extrapyramidal side effects more frequently positive in the metoclopramide arm). Constipation seems, as expected, to be more frequent among patients in the setron arm *(P* <0.05). Restlessness and sleeplessness were more frequent with metoclopramide arm.

Table (8): Toxicities during antiemetic treatment.

Toxicity	Ondan+dexa (*n* = 52)	Meto+dexa (*n* = 48)	Total (*n* = 100)
Epigastric pain	4 (8%)	4 (7%)	8 (8%)
Restlessness	1 (2%)	3 (6%)	4 (4%)
Abnormal movements	3 (6%)	1 (2%)	4 (4%)
Sleeplessness	2 (4%)	5 (11%)	7 (7%)
Constipation	20 (38%)	13 (28%)	33 (33%)
Headaches	10 (19%)	9 (18%)	19 (19%)
Asthenia	5 (10%)	4 (8%)	9 (9%)
Any others	12 (23%)	14 (29%)	26 (26%)

Discussion

The aim of this study was to observe whether patients without acute emesis benefited from a setron, compared with metoclopramide, each in combination with a corticosteroid, for control of delayed emesis. In the present study, the rate of control for acute emesis by i.v. ondansetron with dexamethasone was very high (86%) and comparable to that obtained by i.v. metoclopramide with dexamethasone (85%) as shown in table (3). The rate of acute emesis (14% severe nausea or vomiting) obtained with setron and corticosteroid combination was lower than the 20–25% anticipated in the protocol previously reported by others [1], confirming the high degree of protection from acute emesis.

These well controlled patients also had control of delayed emesis in 81% of ondansetron and 84% of metoclopramide treated cases (table 5). Thus, we confirm that preventative treatment of delayed emetic-chemotherapy-induced nausea and vomiting depends on the rate of control during

the acute phase of treatment. Patients experiencing acute emesis had poor control in the delayed phase.

The analytic tables for the present study (table 4,6) allow full understanding of the results, especially in relation to the rate of acute control and its influence on delayed emesis, per type of chemotherapy and randomization. Such tables should be available for all studies of delayed emesis, as obviously these variables play a major role in the overall results.

The present study does not allow one to conclude with confidence regarding a lack of difference between the approaches in patients who had nausea and vomiting on day 1, as the numbers are small. However, other studies have not shown any superiority of the addition of a setron to dexamethasone for these patients [7, 8]. The Italian Group for Antiemetic Research has shown that,for patients receiving cisplatin-based chemotherapy who have no acute emesis, metoclopramide and ondansetron are of similar efficacy during the delayed phase [7]. In those patients who had acute emesis, ondansetron prevented delayed emesis in only 29% of cases, compared to 4% for metoclopramide. However, if one accounts for severe nausea, no difference is observed between the arms during the delayed phase. Meanwhile, the present clinical trial does not show any statistically significant difference (p>0.05) between both treatment arms and the confidence intervals for nausea and vomiting control in these arms overlap to a large extent during acute and delayed emesis (table 7).

For those patients receiving moderately emetic chemotherapy and experienced acute emesis, the Italian Group compared oral placebo to oral ondansetron 8 mg, both combined with dexamethasone 4 mg orally bid, on days 2–5 after the start of chemotherapy [8]. The delayed complications were prevented in 18 of the 44 patients taking the combination of the two drugs (41%) and in 10 of the 43 patients on dexamethasone alone (23%). The authors concluded that the best choice for preventing delayed nausea and vomiting in patients at high risk for these complications remains to be identified. Other papers offer contradictory results in this field, but they were not prospectively designed to take into account the influence of acute emesis on the rate of control of delayed emesis [1,9].

In this study, many patients had moderately emetic chemotherapy and an excellent rate of acute control with i.v. ondansetron (8 mg) and i.v. dexamethasone (8 mg). However, emerging data indicate that a 4 mg ondansetron dose may be sufficient for such patients [10]. The 8 mg dose of dexamethasone used in this study for acute emetic control might be low for patients receiving cisplatin-based chemotherapy, where 20 mg has been suggested as a standard [11]. However, for the majority of our patients, this combination was excellent, with an 86% acute control rate. The doses of dexamethasone and metoclopramide used in this study are not those suggested by other authors for use with cisplatin-based chemotherapy [12]. They are based on a clinical practice consensus.

The partial control of nausea and vomiting resulted from this trial and other previous reports support the said that additional mechanisms, not involving $5HT_3$ receptors, may play a role in chemotherapy induced delayed emesis. The development of neurokinin-1 receptor antagonists (e.g. aprepitant) might be of major importance in this setting [13].

All antiemetics used in the present study were well tolerated. It was very difficult to differentiate the side effects due to chemotherapy from those due to antiemetics used since both were given concurrently. Abnormal movement and constipation observed more in patients receiving ondansetron (table 8), as reported with previous studies [9,10]. It is noteworthy that sever extrapyramidal side effects did not occur in any of the patients receiving metoclopramide. The dose of metoclopramide used in the present study appears not to produce acute dystonic reactions in adult patients.

Conclusion

Administration of i.v. ondansetron with dexamethasone achieves an extremely high control of acute emesis. For delayed emesis control, the routine prescription of oral setrons is not advisable as it increases cost without any benefit over metoclopramide for the majority of patients. Patients should be offered a combination of a corticosteroid and metoclopramide for duration from 2 to 6

days. Delayed emesis in the rare patients with acute phase emesis remains an unsolved problem. However, further studies with large sample size are needed to confirm these findings.

References

1. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the Perugia Consensus Conference. Antiemetic Subcommittee of the Multinational Association for Supportive Care in Cancer (MASCC). Ann Oncol 2005; 9: 811–819.
2. Gralla RJ, Navari RM, Hesketh PJ et al. Single-dose oral granisetron has equivalent antiemetic efficacy to intravenous ondansetron for highly emetogenic cisplatin-based chemotherapy. J Clin Oncol 2006; 16: 1568–1573.
3. Perez EA, Hesketh P, Sandbach J et al. Comparison of single-dose oral granisetron versus intravenous ondansetron in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy: a multicenter, double-blind, randomized parallel study. J Clin Oncol 2009; 16: 754–760.
4. Bernhard J, Maibach R, Thürlimann B et al. Patients' estimation of overall treatment burden: why not ask the obvious? J Clin Oncol 2002; 20: 65–72.
5. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979; 35: 549–556.
6. Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrics 1983; 70: 659–663.
7. Ondansetron versus metoclopramide, both combined with dexamethasone, in the prevention of cisplatin-induced delayed emesis. The Italian Group for Antiemetic Research. J Clin Oncol 2007; 15: 124–130.
8. Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. The Italian Group for Antiemetic Research. N Engl J Med 2000; 342: 1554–1559.
9. Friedman CJ, Burris HA 3rd, Yocom K et al. Oral granisetron for the prevention of acute late onset nausea and vomiting in patients treated with moderately emetogenic chemotherapy. Oncologist 2000; 5: 136–143.
10. Hesketh PJ, Crews JR, Cohen R et al. Antiemetic efficacy of single-dose oral granisetron (1 mg vs 2 mg) with moderately emetogenic chemotherapy. Cancer J Sci Am 2000; 6: 157–166.
11. Double-blind, dose-finding study of four intravenous doses of dexamethasone in the prevention of cisplatin-induced acute emesis. Italian Group for Antiemetic Research. J Clin Oncol 2008; 16: 2937–2942.

12. Kris MG, Gralla RJ, Tyson LB et al. Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. J Clin Oncol 2009; 7: 108–114.
13. Diemunsch P, Grelot L. Potential of substance P antagonists as antiemetics. Drugs 2000; 60: 533–546.