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A Comparison of Ondansetron with Metoclopramide in the Prophylaxis of Chemotherapy-induced Nausea and Vomiting: A Randomized, Double-blind Study

STEIN KAASA, STEIN KVALØY, MARIO A. DICATO, FERNAND RIES, JOHN V. HUYS, ERIC ROYER, LINDA CARRUTHERS and the International Emesis Study Group

Abstract—*The efficacy of ondansetron was compared with metoclopramide in the prophylaxis of nausea and vomiting induced by cyclophosphamide* ≥ 500 mg/m² *in combination with doxorubicin* ≥ 40 mg/m² *or epirubicin* ≥ 40 mg/m². *Complete anti-emetic protection in the* 24 h *following chemotherapy was achieved in* 26 *of* 40 (65%) *patients treated with ondansetron compared with* 17 *of* 42 (41%) *patients treated with metoclopramide. Severe nausea was present in* 3% *of patients in the ondansetron group and* 31% *in the metoclopramide group. A worst day analysis of control of emesis and nausea on days* 2 *and* 3 *following chemotherapy also demonstrated ondansetron to be more effective than metoclopramide. Both treatments were well tolerated. Ondansetron is more effective as an anti-emetic than metoclopramide in this type of cytostatic therapy.*

INTRODUCTION

NAUSEA AND VOMITING are among the most unpleasant side-effects of cancer chemotherapy. These symptoms are not only distressing for the patient but may also result in metabolic complications including dehydration, electrolyte imbalance, alkalosis and malnutrition. Moreover, the morbidity induced may lead to premature termination of potentially curative chemotherapy [1].

Chemotherapy regimens containing cyclophosphamide and doxorubicin or epirubicin frequently result in vomiting persisting for up to 48 h and nausea often continuing for several days [2]. A previous study in patients treated with the combination of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) reported nausea and vomiting in more than 80% of patients [3].

None of the currently available anti-emetic agents is entirely effective in preventing emesis. Metoclopramide is the most commonly used agent, however its use has been associated with a number of side-effects including sedation [4] and extrapyramidal reactions such as akathisia and/or acute dystonia [5].

Ondansetron is a novel, highly selective $5HT_3$ antagonist [6]. It has been shown to be both highly effective in the prophylaxis of nausea and vomiting induced by cisplatin [7, 8] and by non-cisplatin chemotherapy regimens [9–11].

The aim of this double-blind study was to compare the efficacy and safety of ondansetron with a standard anti-emetic medication, metoclopramide, in the prophylaxis of nausea and vomiting induced by cancer chemotherapy regimens containing cyclophosphamide together with doxorubicin or epirubicin. The effectiveness of ondansetron and metoclopramide was determined for at least 3 days following cancer chemotherapy.

MATERIALS AND METHODS

Patient population

Male and female patients on their first course of chemotherapy, who were to receive cyclophospham-

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Address reprint requests to Prof. M. Dicato, at the Centre Hospitalier de Luxembourg, Luxembourg.
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The International Emesis Study Group consisted of the following participating centres, investigators and collaborators—Det Norske Radium Hospital, Olso, Norway: Stein Kaasa, M.D., Stein Kvaløy, M.D., Grete Lauvvang; Centre Hospitalier de Luxembourg, Luxembourg: Mario A. Dicato, M.D., Fernand Ries, M.D.; U.Z. Gent, Gent, Belgium: John V. Huys M.D.; Hôpital St Joseph, Gilly, Belgium: Eric Royer, M.D., Jean J. Brynaert, M.D., Françoise Gilsoul, M.D.; A.Z. St Jan, Brugge, Belgium: Albert Clarysse, M.D.; Clinique Saint Pierre, Ottignies, Belgium: Pierre FF Duprez, M.D.; Hôpital de la Citadelle, Liege, Belgium: Chantal André, M.D.; Clinque Ste. Elizabeth, Liege, Belgium: Christian Focan, M.D.; Hôpital Civil, Marchienne-au-Pont, Belgium: J.P. Dumont, M.D.; Cliniques Universitaires St. Luc, Bruxelles, Belgium: Jacques Longueville, M.D.; Royal Victoria Infirmary, Newcastle-upon-Tyne, U.K.: Stephen J. Proctor, M.D., Penny Taylor, M.D.; Western General Hospital, Edinburgh, U.K.: John F. Smyth, M.D., Mary O'Brien, M.D.; Glaxo Group Research, Middlesex, U.K.: Linda Carruthers PhD.; Glaxo Belgium S.A., Bruxelles, Belgium: Alain Vandenberghe, M.D., Danielle Sautois, PhD.; Glaxo A/S, Oslo, Norway: Ellen-Karine Qvigstad, M.Sc.

ide ≥ 500 mg/m^2, plus doxorubicin ≥ 40 mg/m^2 or epirubicin ≥ 40 mg/m^2, either alone or in combination with other agents, were entered into the study.

Patients were excluded from the study if they had severe concurrent illness other than neoplasia or if they experienced anticipatory emesis. Patients who were to receive cisplatin, dacarbazine, or any other anti-emetic agents were also not admitted into the study.

Anti-emetic regimen

After explaining the purposes of the study and obtaining consent, patients were randomly assigned to receive either ondansetron (8 mg) by intravenous infusion followed by 8 mg orally 3 times daily or metoclopramide (60 mg) by intravenous infusion followed by 20 mg orally 3 times daily. The intravenous loading dose was given 15 min prior to chemotherapy and the first oral dose was taken 4 h after chemotherapy. Oral treatment was administered for a maximum of 3 days with the option of extending the treatment for a further 2 days if symptoms persisted.

Evaluation

Diary cards documenting both the number of vomits and the number of dry retches, were completed daily (retrospectively for the previous 24 h) by patients, for up to 5 days following chemotherapy. An emetic episode was defined as a single vomit or a dry retch. The intensity of nausea was graded by patients according to how it interfered with daily life, namely:

none
mild —did not interfere with normal daily life
moderate —interfered with normal daily life
severe —bedridden due to nausea.

Any other upsetting symptoms noted on the diary cards were assessed and adverse effects were documented accordingly. Biochemical and haematological tests were carried out to evaluate safety of the study drugs.

Statistical analysis

Emetic responses were categorized as follows:

complete response (0 emetic episodes)
major response (1–2 emetic episodes)
minor response (3–5 emetic episodes)
failure (> 5 emetic episodes or given rescue medication).

Emetic responses and grades of nausea were analysed using Mantel–Haenzel's chi-squared test. The number of emetic episodes were analysed by non-parametric methods using Wilcoxon rank sums.

RESULTS

Ninety-three patients (74 women, 19 men) of median age 58 years (range 19–80 years) were entered into the study. Of these patients, 51 received chemotherapy for breast cancer, 31 for non-Hodgkin's lymphoma and 11 for other tumour types. All prognostic factors were well balanced between the two study treatments.

Acute emesis and nausea

Grades of emetic response, related to vomits plus dry retches, and intensity of nausea, for the 24 h following chemotherapy are reported in Table 1.

Thirty-two of the 40 evaluable patients given ondansetron (80%) experienced two or less emetic episodes compared with 26 of the 42 patients (62%) treated with metoclopramide ($P = 0.074$). More patients had complete control of emesis with ondansetron (65%) compared with metoclopramide (41%), where $P = 0.027$. Indeed, only three patients (8%) given ondansetron were considered treatment failures, whereas 14 patients (33%) failed to respond to metoclopramide. Vomiting alone was successfully controlled (complete and major responses) in 37 out of the 40 patients (93%) given ondansetron, compared with 30 of 42 patients (71%) treated with metoclopramide. These results were signficantly in favour of ondansetron, $P = 0.014$.

Markedly fewer patients experienced nausea following treatment with ondansetron, with 34 of the 40 (85%) patients experiencing no or mild nausea following treatment with ondansetron and 24 of the 42 patients (57%) following treatment with metoclopramide ($P = 0.008$). It should be noted that only one patient receiving ondansetron experienced severe nausea whereas 13 patients given metoclopramide experienced severe nausea.

Delayed emesis and nausea

On the worst day of days 2 and 3 following chemotherapy, 29 of 38 patients treated with

Table 1. Incidence of emesis (vomits plus retches) and nausea in the 24 h following chemotherapy

	Ondansetron	Metoclopramide
Number of evaluable patients	40	42
Complete anti-emetic protection	26 (65%)	17 (41%)
Major anti-emetic protection (1–2 emetic episodes)	6 (15%)	9 (21%)
Minor anti-emetic protection (3–5 emetic episodes)	5 (13%)	2 (5%)
Failure (> 5 emetic episodes)	3 (8%)	14 (33%)
Nausea—none	19 (48%)	13 (31%)
mild	15 (38%)	11 (26%)
moderate	5 (12%)	5 (12%)
severe	1 (3%)	13 (31%)

ondansetron (76%) experienced complete or major control of emesis, compared with 25 of 37 patients treated with metoclopramide (68%).

Nausea was also less pronounced following treatment with ondansetron; with 28 of 38 patients (74%) experiencing no or mild nausea, compared with 24 of 37 patients (65%) given metoclopramide. None of these differences were statistically significant.

Overall response

A comparison of the overall responses, using the worst day of the 3 days following chemotherapy, demonstrated ondansetron to be superior to metoclopramide with regard to the grade of emetic response (complete or major control of emesis was reported in 26 of 40 patients following ondansetron, compared with 23 of 42 following metoclopramide). The numbers of vomits plus retches were significantly lower with ondansetron as shown in Table 2 ($P = 0.026$). Nausea was absent or mild in 28 of 40 patients given ondansetron compared with 22 of 42 patients given metoclopramide ($P = 0.121$).

Safety

Both treatments were well tolerated. Only two patients, both of whom had received metoclopramide, experienced symptoms including restlessness, heart palpitation, and anxiety, consistant with extrapyramidal reactions, leading to the discontinuation of the study drug. Transient headache was reported in four patients treated with ondansetron. There were no abnormalities in biochemical or haematological parameters considered to be related to either ondansetron or metoclopramide.

Table 2. Incidence of emesis (vomits plus retches) and nausea on the worst day in the 3 days following chemotherapy

	Ondansetron	Metoclopramide
Number of evaluable patients	40	42
Complete anti-emetic protection	21 (52.5%)	13 (31%)
Major anti-emetic protection (1–2 emetic episodes)	5 (12.5%)	10 (23.8%)
Minor anti-emetic protection (3–5 emetic episodes)	9 (22.5%)	3 (7.1%)
Failure (> 5 emetic episodes)	5 (12.5%)	16 (38.1%)
Nausea—none	13 (32.5%)	12 (28.6%)
mild	15 (37.5%)	10 (23.8%)
moderate	8 (20%)	7 (16.7%)
severe	4 (10%)	13 (31.0%)

DISCUSSION

Chemotherapy regimens containing cyclophosphamide together with doxorubicin or epirubicin are frequently used in the treatment of a variety of cancers. However, the nausea and vomiting induced by these compounds can be so severe that they lead to premature termination of potentially curative therapy [12, 13]. Control of chemotherapy-induced emesis is therefore essential for patient acceptance of therapy.

The results of this study have shown ondansetron to be significantly more effective than metoclopramide, at the dosages used, in the prophylaxis of nausea and vomiting induced by regimens containing cyclophosphamide and doxorubicin/epirubicin.

Maximal emesis occurs within a 24-h period following treatment with cyclophosphamide or anthracyclines [14], and affects over 80% of patients [2 15]. In the present study, on day 1 of treatment, vomiting was successfully controlled (complete and major responses) in 37 of 40 patients given ondansetron, compared with 30 of 42 treated with metoclopramide. When considering an emetic episode as a vomit or a retch, 32 of 40 patients were successfully treated with ondansetron compared with 26 of 42 with metoclopramide. This reduction in the success rate emphasizes the importance of including the number of retches in the evaluation of emetic response.

Ondansetron was also significantly superior to metoclopramide in controlling nausea during day 1 of treatment. Nausea was absent or mild in 34 of 40 patients treated with ondansetron compared with 24 of 42 patients given metoclopramide.

Chemotherapy-induced emesis may persist for 2–3 days (delayed emesis), but nausea often continues for several days [2, 16]. A worst day analysis of complete and major response based on vomiting and retching, again demonstrated ondansetron to be more effective than metoclopramide (29 of 38 compared with 25 of 37 respectively). During this period, nausea was absent or mild in 28 of 38 patients given ondansetron and in 24 of 37 of those given metoclopramide.

Overall analysis of emesis on the worst day of days 1–3 showed the number of vomits or vomits plus retches to be significantly lower in patients treated with ondansetron compared with metoclopramide. In addition, the incidence of severe nausea was markedly less in patients treated with ondansetron than with metoclopramide (10% and 31%, respectively). Only four of the 40 patients given ondansetron experienced severe nausea compared with 13 of 42 given metoclopramide.

Both treatments were well tolerated. Two patients treated with metoclopramide experienced symptoms consistent with extrapyramidal reactions, namely anxiety and/or restlessness, which necessitated their withdrawal from the study. Extrapyramidal reactions are usually associated with younger

patients (≤ 30 years old) following treatment with metoclopramide [17]. As the median age of patients in this study was 58 years, the low incidence of such events was not entirely unexpected. There were no significant differences between ondansetron and metoclopramide with regard to haematological or clinical chemistry parameters.

It may be concluded that ondansetron at a loading dose of 8 mg given intravenously followed by 8 mg given orally, 3 times daily for 3–5 days was well tolerated and showed superior efficacy to metoclopramide in the prophylaxis of nausea and vomiting induced by regimens containing cyclophosphamide together with doxorubicin or epirubicin. Furthermore, the convenient ondansetron dosage schedule and excellent safety profile indicate that it may be used as an effective adjuvant to cancer chemotherapy for out-patient use.

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