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Double-blind Randomised Trial of the Antiemetic Efficacy and Safety of Ondansetron and Metoclopramide in Advanced Breast Cancer Patients Treated with Epirubicin and Cyclophosphamide

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Ondansetron was compared with metoclopramide for antiemetic efficacy in a randomised double-blind trial in 122 patients with advanced breast cancer. All patients were treated with epirubicin (> 50 mg/m²) and cyclophosphamide (> 500 mg/m²). 50 patients receiving ondansetron and 60 with metoclopramide were considered evaluable. Ondansetron was at least as effective as metoclopramide in the control of vomiting and nausea. The percentage of patients with complete plus major control was 72% (59–85%) vs. 61% (48–74%) on day 1 ($P = 0.230$) and 79% (67–91%) vs. 66% (53–78%) on days 2–3 after chemotherapy ($P = 0.122$). Over the 3-day study period, nausea was absent or mild in 60% of the patients treated with ondansetron, compared to 45% given metoclopramide ($P = 0.064$). No major drug-related side-effects were reported. 1 patient receiving ondansetron experienced gastrointestinal disturbance and headache. Episodes of diarrhoea, fever, hyperkinetic syndrome, fatigue, restlessness and migraine with vomiting were reported by 5 patients treated with metoclopramide. None of the changes in the biochemical or haematological parameters was attributed to the antiemetic treatments.
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INTRODUCTION

CYCLOPHOSPHAMIDE-CONTAINING combinations have contributed significantly in the treatment of patients with disseminated breast cancer [1].

Nausea and vomiting, however, are well known side-effects of chemotherapy. Over 80% of patients receiving the combination 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) [2] or cyclophosphamide, methotrexate and 5-fluorouracil

(CMF) [3] are reported to experience these symptoms. Emesis caused by cyclophosphamide does not usually occur until 6–12 hours after administering the cytotoxic. Although vomiting has usually decreased by 24 hours, nausea often persists for 48–72 hours [4]. Prolonged bouts of vomiting cause dehydration and electrolyte imbalance and may cause patients to discontinue a chemotherapeutic regimen.

Emesis associated with non-cisplatin chemotherapy is less severe than with cisplatin and a number of antiemetic drugs are currently in use as single agent therapy. Comparative trials with agents such as metoclopramide, dexamethasone, methylprednisolone, domperidone, nabilone, chlorpromazine or prochlorperazine have demonstrated variable efficacy in 26–85% of patients [5–7]. Furthermore, deployment of any intravenous dosing regimen is not convenient for outpatient treatment.

Metoclopramide is one of the most widely used of the currently available antiemetics. Given orally at 20 mg 8-hourly, emesis was controlled in 26% of patients receiving non-cisplatin chemotherapy [7]. However, when dosed intravenously (10–60 mg) prior to chemotherapy and orally (10–60 mg/day) thereafter, 47% of patients were reported free from emesis [8]. Currently, high doses of intravenous metoclopramide with or without agents such as dexamethasone have proved to be partially successful [9, 10]. However, significant toxicity, in particular extrapyramidal effects with metoclopramide have been encountered particularly in patients less than 30 years old [9].

Recent studies have indicated that chemotherapy causes an increased release of 5-hydroxytryptamine (5-HT) by damaging the gastrointestinal mucosa [11, 12]. The released 5-HT initiates the vomiting reflex by activating 5-HT-3 receptors located centrally (in the area postrema) or those present on peripheral afferent vagal nerve fibres which project into the area postrema [13]. Ondansetron is an antiemetic compound that acts by selective 5-HT-3 receptor antagonism and possesses no dopamine receptor activity [14]. It has been shown to be effective in preventing nausea and emesis in patients receiving cisplatin [15], or non-cisplatin chemotherapy [16, 17] and radiotherapy [18]. In a recent pilot study, ondansetron 8 mg three times daily given orally for 5 days prevented acute emesis in 72% of patients given intravenous cyclophosphamide regimens (> 600 mg/m^2) and provided complete plus major protection (0–2 episodes of vomits or retches) in 85% of patients over the 5-day study period [19].

In this study, the efficacy and safety of ondansetron was compared with metoclopramide, in the prophylaxis of nausea and vomiting caused by chemotherapy regimens containing epirubicin and cyclophosphamide (EC).

PATIENTS AND METHODS

This was a multicentre, randomised, double-blind study, approved by the Schleswig Holstein Ethics Committee, Germany. Patient consent was obtained throughout.

Female patients aged 18 years or over, who were scheduled to receive their first cycle of EC (intravenous epirubicin > 50 mg/m^2 and intravenous cyclophosphamide > 500 mg/m^2) with or without 5-fluorouracil (5-FU) in their current course of chemotherapy. Patients who had previously received non-EC containing adjuvant chemotherapy for breast cancer were also eligible.

Patients were not included if they were pregnant; suffered of severe concurrent illnesses other than neoplasia; were clinically jaundiced; were receiving concurrent benzodiazepines; or had vomited or received antiemetics in the previous 24 hours.

At entry, demography, clinical history, chemotherapeutic schedule and relevant pretreatment symptoms of the patients were recorded. Baseline nausea was assessed and graded as none, mild, moderate or severe. Patients were randomised to receive ondansetron (2 × 4 mg) or matched placebo (× 2) tablets (1–2 hours prior to chemotherapy) followed by a placebo infusion (100 ml saline) or metoclopramide infusion 15 min before chemotherapy (60 mg/100 ml saline). Oral antiemetic medication was continued 8-hourly thereafter with ondansetron (2 × 4 mg) or matched metoclopramide (2 × 10 mg) tablets for 3 days and for up to 5 days if symptoms persisted. The selected dosing for metoclopramide corresponded to typical metoclopramide doses for non-cisplatin chemotherapy.

Each patient completed a diary card daily for up to 5 days to record number of vomiting episodes, grade of nausea, number of tablets taken and any other upsetting symptoms. The patients returned to the clinic after 1 week for clinical assessment. Blood samples for routine haematological and biochemical analyses were taken before treatment, at the 1 week visit and approximately 2–4 weeks later.

The control of acute emesis (day 1), the "worse day" outcome for delayed emesis (days 2–3) and the "worst day" outcome for the overall study period (days 1–3) were assessed as: complete response (0 emetic episodes), major response (1–2 emetic episodes), minor response (3–5 emetic episodes) or failure (> 5 emetic episodes). An emetic episode was either one vomit or one retch. A worst day analysis showed differences between treatments in failing to control emesis. The treatments were compared using the Mantel–Haenzel χ^2 test. Estimates of probability of a success were derived together with 95% confidence intervals. The number of emetic episodes were analysed by non-parametric methods using Wilcoxon rank sums. Grades of nausea were analysed using an extended Mantel–Haenzel method [20].

RESULTS

A total of 122 patients with breast cancer and median age 53 years (range 28–79) were entered. 56 patients commenced

Table 1. Patients' characteristics and chemotherapy regimen

Treatment	Ondansetron	Metoclopramide
Number of patients	56	66
Median age (range) (yr)	55 (28–79)	53 (29–77)
Mean weight (kg) (S.D.)	67.2 (10.2)	66.0 (10.1)
Mean height (cm) (S.D.)	159.9 (5.9)	162 (6.4)
Mean surface area (m^2) (S.D.)	1.7+/−0.12	1.7+/−0.13
No. of patients evaluable for efficacy	50	60
Cyclophosphamide		
Median dose (mg/m^2) (range)	515 (485–625)	516 (471–625)
Epirubicin		
Median dose (mg/m^2) (range)	52 (48–120)	52 (47–124)

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Table 2. Patients withdrawn from efficacy analysis (day 1)

Reason	No. of patients: Ondansetron	Metoclopramide
Day 1		
Epirubicin or cyclophosphamide < 90% permissible dose	1	2
Concurrent steroids	4	–
Previous FEC	–	1
Non-compliance with study drug(s)	1	2
Other*	–	1
Day 2		
Withdrawn by investigator	2	1
Patient stopped treatment	–	1

*Erroneous miscalculation of epirubicin dose.

treatment with ondansetron and 66 with metoclopramide. The median epirubicin and cyclophosphamide doses and patients' demographic details for the respective groups are given in Table 1. 5-FU was added to the EC regimen for 16 patients receiving ondansetron and 12 on metoclopramide.

Those patients considered major protocol violators and therefore unevaluable for efficacy analyses over days 1–3 were withdrawn prior to unblinding the treatment codes. 12 patients (6 ondansetron; 6 metoclopramide) were withdrawn from day 1 analyses as were a further 4 patients (2 on each antiemetic) for the day 2 and 3 analyses. The reasons for withdrawal/unevaluability for day 1 analyses are detailed in Table 2. The 4 patients withdrawn from days 2–3 analyses failed to respond to the antiemetic therapy. 3 were withdrawn by the investigator and got rescue medication, 1 stopped treatment by herself. No patient in both groups was withdrawn due to drug toxicity. A total of 62 patients (30 on ondansetron and 32 on metoclopramide) continued antiemetic treatment to day 4, and 47 patients (23 and 24, respectively) continued to day 5.

The results for the control of nausea and vomiting are listed in Tables 3 and 4. They were divided into acute emesis/nausea (day 1) and delayed emesis/nausea (days 2–3). Furthermore, the incidences were noted for nausea and vomiting regarding the whole study period in a "worst day" analysis (days 1–3). Details of the control of emesis regarding vomits and retches on day 1 and "worst day" analysis of days 2–3 and days 1–3 are shown in Table 3. On day 1, 36/50 (72%; 59–82%) of patients receiving ondansetron experienced complete or major control of acute emesis compared with 36/59 (61%; 48–74%) treated with metoclopramide ($P = 0.230$). Complete plus major control of vomiting alone was achieved in 80% (69–91%) of patients given ondansetron compared with 72% (60–83%) receiving metoclopramide ($P = 0.314$). These differences were not statistically significant. For the "worse day" analysis of the delayed emesis period, days 2–3, 79% (67–91%) of patients receiving ondansetron had complete or major control compared to 66% (53–78%) receiving metoclopramide ($P = 0.122$). Over the study period as a whole (days 1–3) 62% (48–76%) ondansetron patients compared to 50% (37–63%) of metoclopramide patients had complete or major control of emesis ("worst day" analysis, $P = 0.209$). Statistical analyses did not show these differences to be significant. Interestingly, 22% of the patients on metoclopramide experienced > 5 emetic episodes compared with 8% of patients receiving ondansetron ($P = 0.209$).

Table 3. Control of emesis by ondansetron and metoclopramide

Emetic episode (1 vomit or 1 retch)	Complete (0)	Major (1–2)	Minor (3–5)	F/R (> 5)	Patients
Emesis (vomiting and retching)					
Day 1					
Ondansetron	30 (60)	6 (12)	5 (10)	9 (18)	50
Metoclopramide	28 (47)	8 (14)	11 (19)	12 (20)	59*
					(P=0.230)
Days 2–3 worse day (delayed emesis)					
Ondansetron	27 (56)	11 (23)	6 (13)	4 (8)	48
Metoclopramide	25 (44)	13 (22)	7 (12)	13 (22)	58
					(P=0.122)
Days 1–3 worst day analyses (whole study period)					
Ondansetron	23 (46)	8 (16)	8 (16)	11 (22)	50
Metoclopramide	19 (32)	11 (18)	10 (17)	20 (33)	60
					(P=0.209)
Vomiting					
Control of vomiting (day 1)					
Ondansetron	36 (72)	4 (8)	6 (12)	4 (8)	50
Metoclopramide	36 (60)	7 (11.7)	10 (16.7)	7 (11.7)	60
					(P=0.314)
Control of vomiting (days 1–3)					
Ondansetron	32 (64)	6 (12)	6 (12)	6 (12)	50
Metoclopramide	26 (43)	11 (18)	11 (18)	12 (20)	60
					(P=0.031)

F/R = failure or rescue.
No. (%).
*One patient did not provide a record of retches and was excluded from analysis.

Details of the control of nausea are given in Table 4. On day 1 (acute nausea) 69% of patients receiving ondansetron graded their nausea as none or mild compared with 61% on metoclopramide ($P = 0.081$). The outcome of the "worse day" analysis over days 2–3 showed no or mild nausea in 67% of ondansetron and 55% of metoclopramide-treated patients ($P = 0.150$). Over the whole study period (days 1–3) 60% of the patients on ondansetron reported nausea as absent or mild compared with those receiving metoclopramide (45%) ($P = 0.064$). The difference in acute nausea and the differences in the "worst day" analyses for days 2–3 (delayed nausea) and days 1–3 (whole study period) were not statistically significant.

30 patients continued ondansetron treatment up to day 4 and 23 up to day 5. All of these patients had complete or major

Table 4. Control of nausea by ondansetron and metoclopramide

Nausea	None	Mild	Moderate	Severe	Patients
Day 1 (acute nausea)					
Ondansetron	24 (49)	10 (20)	8 (16)	7 (14)	49
Metoclopramide	17 (28)	20 (33)	8 (13)	15 (25)	60
					(P=0.056)
Days 2–3 (delayed nausea) "worse day" analysis					
Ondansetron	18 (38)	14 (29)	13 (27)	3 (6)	48
Metoclopramide	15 (26)	17 (29)	20 (34)	6 (10)	58
					(P=0.150)
Days 1–3 (whole study period) "worst day" analysis					
Ondansetron	15 (30)	15 (30)	11 (22)	9 (18)	50
Metoclopramide	10 (17)	17 (28)	16 (27)	17 (28)	60
					(P=0.064)

No. (%).

control of emesis. Of the 32 metoclopramide patients who continued to day 4, 84% had complete or major control of emesis as did 95% of the 24 patients continuing treatment up to day 5. In both groups nausea was graded as none or mild by more than 80% of patients.

No major drug-related side-effects were reported. 1 patient receiving ondansetron experienced gastrointestinal disturbance and headache. Episodes of diarrhoea, fever, hyperkinetic syndrome, fatigue, restlessness and migraine with vomiting were reported by a total of 5 patients treated with metoclopramide. None of the changes in the biochemical or haematological parameters was attributed to antiemetic treatment.

DISCUSSION

Complete or major control of vomiting or retching over the first 24 hours following chemotherapy was achieved in 72% (59–85%) of patients given ondansetron and in 61% (48–74%) receiving metoclopramide. The difference between treatments did not reach statistical significance ($P = 0.230$).

Ondansetron was at least as effective as metoclopramide. During the acute phase, the onset and severity of nausea usually follows the pattern for emesis. Hence, its control is equally important for the patient's well-being and comfort.

In the present study no or mild nausea on day 1 was achieved in 69% of ondansetron-treated and 61% of metoclopramide-treated patients. The data for the control of acute nausea and emesis are consistent with the literature, which showed either an equal antiemetic efficacy or superiority of ondansetron in comparison to the standard antiemetic metoclopramide in the control of acute emesis [16, 17, 21]. The incidences of delayed emesis and nausea in patients receiving non-cisplatin chemotherapy are not well documented in literature. However, there is evidence that more than 50% of the patients receiving cyclophosphamide remain nauseated for a median of 3–5 days [16]. In the current study, patients continued with the antiemetic medication for at least 3 days.

Our data gave no evidence of a relevant difference in the control of delayed emesis regarding both antiemetics. Both antiemetics were well tolerated. Only one case of hyperkinetic syndrome and one case of restlessness were reported by patients given metoclopramide. This low incidence of the possible dystonic reactions may be explained by the fact that the median age of patients recruited into this study was 53 years. Dystonic reactions are known to occur more frequently in patients aged below 30 years. The absence of any symptoms related to the dopaminergic system in patients given ondansetron confirms its high selectivity for 5-HT_3 receptors.

In conclusion, ondansetron given orally was well-tolerated and at least as effective as metoclopramide in preventing nausea and vomiting associated with EC therapy. Its simple and convenient dosing schedule can be beneficial in the supportive management of outpatients.

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