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5-HT_3 Receptor Antagonists in the Prophylaxis of Acute Vomiting Induced by Moderately Emetogenic Chemotherapy—A Randomised Study

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166 patients receiving moderately emetogenic chemotherapy were entered into a randomised prospective study in which the efficacy of single dose ondansetron 8 mg, tropisetron 5 mg and granisetron 3 mg in the prophylaxis of acute vomiting was evaluated. 130 patients were evaluable for analysis. During the 24 h following the start of chemotherapy complete control of vomiting was achieved in 80% [95% confidence interval (CI) 73.1; 86.9] of patients receiving granisetron compared with 75% (95% CI 67.1; 82.1) of those on tropisetron and 69% (95% CI 60.5; 76.5) on ondansetron. The patients experienced significantly fewer failures with granisetron (6.2%, 95% CI 2.1; 10.3) than with either ondansetron (14.6%, 95% CI 8.5; 20.6) or tropisetron (13.8%, 95% CI 7.9; 19.7). When asked, 34 (26%) patients out of 130 expressed no preference, 54 (42%) preferred granisetron, 22 (17%) preferred ondansetron and 20 (15%) preferred tropisetron. All the 5-HT_3 receptor antagonists were highly effective in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy. The observed differences in the control of emesis, although statistically significant, may not have clinical significance.
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INTRODUCTION

ACUTE NAUSEA and vomiting are the most feared side-effects of cytotoxic chemotherapy [1]. The exact mechanism of chemotherapy-induced emesis is only partly clarified. The discovery of the role of serotonin in chemotherapy-related nausea and vomiting has been a major step in revealing this mechanism [2, 3]. Cytotoxic chemotherapy appears to release serotonin from the upper gastrointestinal tract [4]. The initiation of the emetic reflex may be produced via 5-HT_3 receptors located on vagal afferent nerves in the gut or in the postrema area of the brain [5, 6]. Ondansetron (GR38032F), tropisetron (ICS 205-930) and granisetron (BRL43694) are highly selective 5-HT_3 receptor antagonists with demonstrated antiemetic activity in patients receiving cisplatin- [7–9] and non-cisplatin-containing regimens [10–12]. Current evidence suggests that 5-HT_3 receptor antagonists are at least as effective as high-dose metoclopramide in the acute control of cisplatin-induced emesis [7–9]. Furthermore, 5-HT_3 receptor antagonists have the advantage of showing no tendency to cause sedation or extrapyramidal effects seen with antidopaminergic agents. Constipation and headaches have been the main side-effects assigned to 5-HT_3 receptor antagonists.

Ondansetron has a half-life of 3 h [13]. Doses and schedules of ondansetron have varied in different antiemetic trials. For moderately emetogenic chemotherapy a loading dose of 8 mg orally or intravenously (i.v.) followed by 8 mg every 12 h has been recommended [14]. A single prophylactic dose of ondansetron (8–32 mg i.v.) has been as effective as a continuous infusion schedule (8 mg i.v., then 1 mg/h for 24 h) in controlling acute cisplatin-induced emesis [14]. Tropisetron has a half-life of 8 h and a single 5 mg dose prior to the chemotherapeutic agents has been recommended [15]. The elimination half-life of granisetron is approximately 3–6 h with wide inter-subject differences in kinetics [16]. At present, granisetron is used as a single i.v. injection of 3 mg for all chemotherapeutic regimens [17]. There are also differences in the affinities and specifities of ondansetron, tropisetron and granisetron for 5-HT_3 receptors in different experimental conditions [17, 18]. However, it is not known to what extent these differences are clinically relevant.

We report the results of an open, randomised, multicentre cross-over study of a single dose of ondansetron (8 mg i.v.), tropisetron (5 mg i.v.) and granisetron (3 mg i.v.) in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy.

PATIENTS AND METHODS

The patients were eligible for the study if they were at least 18 years of age and designated to receive three similar subsequent courses of moderately emetogenic chemotherapy as antineoplastic treatment. Exclusion criteria were: vomiting or the use of antiemetic drugs within 24 h prior to chemotherapy, signs of bowel obstruction,verified or suspected CNS tumour or metastases, severe concurrent illness other than neoplasia, use of corticosteroids unless as part of the chemotherapy regimen and use of benzodiazepines, except when given for night sedation. Alcohol intake was not recorded, but patients regarded as having a very high alcohol intake (abusers) were excluded. Both outpatients and inpatients were eligible for the study. Verbal informed consent was obtained from all patients.

Patients who had received previous chemotherapy as well as chemotherapy-naive patients were included in the study. Patients entered the study consecutively and were randomly assigned

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Table 1. Patients' characteristics and chemotherapy administered

No. of patients	166
Males/females	27/139
Mean age (years)	
Males	53.9
Females	49.9
Age range	24–81
Previous chemotherapy	
Yes	117
No	49
Type of malignancy (no. of patients)	
Breast	107
Gastrointestinal	27
Lymphoma	15
Lung	7
Head and neck	3
Mesothelioma	3
Other	4
Chemotherapy	
CMF	
FAC/FEC	56
Cyclophosphamide+mitoxantrone+5-FU	24
Other cyclophosphamide-containing	8
Doxorubicin/epirubicin+MTX+5-FU	12
Other anthracycline-containing	23
Carboplatin-containing	15
Mitomycin+MTX+mitoxantrone	8
DTIC-containing	8
Cisplatin < 50 mg/m^2	3
Other	3
	6

C, cyclophosphamide; M, methotrexatate; F or 5-FU, 5-fluorouracil; A, doxorubicin; E, epirubicin; MTX, methotrexate; DTIC, ductual carcinoma *in situ*.

to receive 5-HT$_3$ receptor antagonists by one of the six possible sequences by a closed letter method. Naive patients and non-naive patients were randomised separately. A loading dose of ondansetron 8 mg, tropisetron 5 mg or granisetron 3 mg was given to the patients by slow i.v. injection immediately before chemotherapy. No other antiemetics were given during the first 24 h after the start of the treatment. From day 2 onwards patients received metoclopramide, 10 mg 6-hourly orally, if experiencing nausea.

An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches. Control of vomiting during the first 24 h was scored as follows: complete: no vomiting or retches; partial: 1–2 vomits or retches; failure: more than two vomits or retches. Nausea was not recorded as an evaluation criteria. Patients completed diary cards for the first 24 h after the start of chemotherapy, recording the number of vomits and retches. After having completed three identical chemotherapy cycles, the patients were asked to indicate their preference, if any, for the study treatments.

Differences between the groups were tested with the χ^2 test of the SPSS-PC statistical software for personal computers. Values of $P < 0.05$ were regarded as statistically significant. 95% confidence intervals were calculated assuming normal distribution of the differences in the percentages.

RESULTS

The characteristics and chemotherapy regimens of the 166 patients entered into the study are shown in Table 1. The response to antiemetic therapy in each cycle is shown in Table 2. 36 patients could not be evaluated in the cross-over analysis of response. 18 of these had their chemotherapy regimens changed because of progressive disease and thus did not fulfil the main study criteria. 4 patients had chemotherapy dose reductions because of low blood counts. Data on emesis was incomplete for 5 patients. 4 patients requested to be withdrawn after the first cycle because of inadequate control of emesis (2 were given ondansetron and 2 tropisetron). 2 patients were lost to follow-up due to emigration. 1 patient did not fulfil the inclusion criteria (astrocytoma). 1 patient received tropisetron twice which was considered a major violation of study protocol, and 1 patient requested to be withdrawn after randomisation.

130 patients were included in the cross-over analysis of response. During the first cycle, 48 patients received ondansetron, 38 tropisetron and 44 granisetron. The respective numbers in the second and third cycles were: ondansetron 46 and 36, tropisetron 44 and 48, granisetron 40 and 46. The response of these patients to antiemetic therapy in three cycles is shown in Table 3. Granisetron was superior to ondansetron in the complete control of vomiting during the first 24 h ($P = 0.034$) and there were also significantly fewer patients expressing failure with granisetron than with ondansetron ($P = 0.026$) or with tropisetron ($P = 0.039$). There was no statistically significant difference between granisetron and tropisetron in the complete control of vomiting. Neither were there statistically significant differences between ondansetron and tropisetron in the complete control or failures. When asked for preference, 34 (26.2%) patients out of 130 expressed no preference, 22 (16.9%) preferred ondansetron, 20 (15.4%) preferred tropisetron and 54 (41.5%) preferred granisetron. Headache was the only adverse event systematically recorded at every cycle. The study drugs did

Table 2. Grade of control of vomiting during the first 24 h in three cycles of moderately emetogenic chemotherapy assessed by cycle (per cent evaluable patients in each cycle)

	Cycle 1 (n = 161)			Cycle 2 (n = 139)			Cycle 3 (n = 130)		
Grade of control	Ondansetron (%)	Tropisetron (%)	Granisetron (%)	Ondansetron (%)	Tropisetron (%)	Granisetron (%)	Ondansetron (%)	Tropisetron (%)	Granisetron (%)
Complete	60.7	74.5	84.0*	73.5	67.4	70.5	69.4	72.9	80.4
Partial	21.4	12.7	14.0	16.3	6.5	15.9	11.1	16.7	10.9
Failure	17.9	12.7	2.0*†	10.2‡	26.1	13.6	19.4	10.4	8.7

*$P < 0.01$ granisetron vs. ondansetron; †$P < 0.05$ granisetron vs. tropisetron; ‡$P < 0.05$ ondansetron vs. tropisetron.

Table 3. Grade of control of vomiting during the first 24 h in three cycles of moderately emetogenic chemotherapy (patients evaluable in all three cycles)

Grade of control	Ondansetron			Tropisetron			Granisetron		
	n	%	(95% CI)	*n*	%	(95% CI)	*n*	%	(95% CI)
Complete	89	68.5	(60.5; 76.5)	97	74.6	(67.1; 82.1)	104	80.0	(73.1; 86.9)
Partial	22	16.9	(10.5; 23.3)	15	11.5	(6.0; 17.0)	18	13.8	(7.9; 19.7)
Failure	19	14.6	(8.5; 20.6)	18	13.8	(7.9; 19.7)	8	6.2	(2.1; 10.3)
Total	130			130			130		

not differ in this respect: 35% with ondansetron, 34% with tropisetron and 35% with granisetron experienced this adverse event.

DISCUSSION

Patients assigned to chemotherapy express fear for mainly two side-effects: loss of hair and vomiting, despite the fact that chemotherapy regimens differ considerably with respect to these unwanted events [1]. The short era of the 5-HT_3 antagonists in clinical use has been associated with a remarkable change in the routine chemotherapy treatment of cancer patients. Even with the highly emetogenic regimens containing cisplatin it is now possible to prevent acute vomiting in most of the patients [19]. However, 5-HT_3 antagonists have not been superior to conventional antiemetics for delayed nausea and vomiting [20]. Most of the antiemetic studies with these drugs have been performed using high-dose cisplatin-containing regimens. This of course is reasonable particularly when comparison trials are concerned.

The role of 5-HT_3 antagonists in the prophylaxis of emesis induced by moderately emetogenic regimens is not clear. The efficacy of 5-HT_3 antagonists with these less emetogenic treatments is good. However, usually a good control of emesis is already achieved with so-called standard antiemetics consisting mainly of metoclopramide and dexamethasone. Nevertheless, it is very unlikely that the use of 5-HT_3 antagonists will be restricted only to chemotherapy including cisplatin. This would not have a sound basis in medical ethics, since the interpersonal differences in experiencing nausea and vomiting are known to be great.

In this study, an excellent complete control rate was achieved with all three trial drugs. However, the failure rate was significantly lower with granisetron. This may be due to the pharmacological differences between these compounds. One feasible explanation could be the higher specificity and affinity of granisetron for 5-HT_3 receptors [17]. Granisetron was preferred by 41% of the patients, correlating well with the highest complete control rate (80%) as well as the lowest failure rate (6.2%).

Methodological problems in clinical antiemetic studies are many [21]. The studies are usually based on a heterogenous group of patients with several different malignancies and stages of disease. As mentioned earlier, the variability in emetic response between the patients can also be outstanding, a problem which especially concerns moderately emetogenic chemotherapy. Furthermore, the efficacy of antiemetic treatment may vary with the treatment course due to anticipatory vomiting and/or patient's altered clinical status. A cross-over design enables the use of the patients as their own controls, thus reducing the variance of a given sample size.

The patients were randomised to six different possible sequences of antiemetic therapy. Thus, theoretically all of them had an equal probability of receiving ondansetron, tropisetron or granisetron as their first, second and third treatment. The assumption was made that by this methodology the effect of anticipatory vomiting could be controlled for. Naturally, the use of the cross-over design is mandatory in order to study preferences among the trial drugs.

We observed minor differences between the three 5-HT_3 antagonists in the control of acute emesis induced by moderately emetogenic chemotherapy. Whether these differences have clinical relevance is a matter of discussion. The drugs did not differ in their potential to cause headache, the most common adverse event assigned to 5-HT_3 receptor antagonists.

1. Coates A, Abraham S, Kaye SB, *et al.* On the receiving end—patient perception of the side-effects of cancer chemotherapy. *Eur J Cancer Clin Oncol* 1983, **19**, 203–208.
2. Fozard JR, Mobarok Ali AT. Blockade of neuronal tryptamine receptors by metoclopramide. *Eur J Pharmacol* 1978, **49**, 109–112.
3. Miner WD, Sanger GJ. Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine m-receptor antagonism. *Br J Pharmacol* 1986, **88**, 497–499.
4. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Finn AL. Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin induced nausea and vomiting. *N Engl J Med* 1990, **322**, 810–816.
5. Richardson BP, Engel G, Donatsch P, Stadler PA. Identification of serotonin M-receptor subtypes and their specific blockade by a new class of drugs. *Nature* 1985, **316**, 126–131.
6. Kilpatrick GJ, Jones BJ, Tyers MB. The identification and distribution of 5-HT_3 receptors in rat brain using radioligand binding. *Nature* 1987, **330**, 746–748.
7. Marty M, Pouillart P, Scholl S, *et al.* Comparison of the 5-hydroxytryptamine3 (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 1990, **322**, 816–821.
8. Sorbe B, Glimelius B, Hansen O, Högberg TH, Pruemm V. A multicenter, randomised study comparing the anti-emetic effects of the 5-HT_3 antagonist ICS 205-930 with a metoclopramide-containing antiemetic cocktail in patients receiving cisplatin chemotherapy. *Ann Oncol* 1990, (Suppl 1), 113.
9. Chevallier B on behalf of the Granisetron Study Group. Efficacy and safety of granisetron compared with high-dose metoclopramide plus dexamethasone in patients receiving high-dose cisplatin in a single-blind study. *Eur J Cancer* 1990, **26** (Suppl 1), S33–S36.
10. Jones AL, Hill AS, Soukop M, *et al.* Comparison of dexamethasone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. *Lancet* 1991, **338**, 483–487.
11. Bregni M, Siena S, Di Nicola M, Bonadonna G, Gianni AM. Tropisetron plus haloperidol to ameliorate nausea and vomiting associated with high-dose alkylating agent cancer chemotherapy. *Eur J Cancer* 1991, **27**, 561–565.
12. Marty M on behalf of the Granisetron Study Group. A comparative study of the use of granisetron, a selective 5-HT_3 antagonist, versus a standard anti-emetic regimen of chlorpromazine plus dexamethasone in the treatment of cytostatic-induced emesis. *Eur J Cancer* 1990, **26** (Suppl. 1), S28–S32.

13. Blackwell CP, Harding SM. The clinical pharmacology of ondansetron. *Eur J Cancer Clin Oncol* 1989, **25** (Suppl. 1), S21–S24.
14. Brown GW, Paes D. Ondansetron: dose schedules and duration of treatment. In Marty M, Pappo M, eds. *Ondansetron and Chemotherapy Induced Emesis*, 3rd International Congress on Neo-adjuvant Chemotherapy. Berlin, Springer. 1991, 53–64.
15. Gamse R. Antiemetic action of 5-HT_3 receptor antagonists: review of preclinical and clinical results with ICS 205–930. *Cancer Treat Rev* 1990, **17**, 301–305.
16. Upward JW, Arnold BD, Link C, Pierce DM, Allen A, Tasker TC. The clinical pharmacology of granisetron (BRL 43694), a novel specific 5-HT_3 antagonist. *Eur J Cancer* 1990, **26** (Suppl. 1), S12–S15.
17. Andrews PL, Bhandari P, Davey PT, Bingham S, Marr HE, Blower PR. Are all 5-HT_3 receptor antagonists the same? *Eur J Cancer* 1992, **28A** (Suppl. 1), S2–S6.
18. Freeman AJ, Cunningham KT, Tyers MB. Selectivity of 5-HT_3 receptor antagonists and anti-emetic mechanisms of action. *Anti-Cancer Drugs* 1992, **3**, 79–85.
19. Smith DB, Newlands ES, Rustin GJ, *et al.* Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containing chemotherapy. *Lancet* 1991, **338**, 487–490.
20. Kaye SB, Khayat D, Aapro M, Diehl V. Who should receive a 5-HT_3 antagonist? *Lancet* 1992, **340**, 1107–1108.
21. Tonato M, Roila F, Del Favero A. Methodology of antiemetic trials: a review. *Ann Oncol* 1991, **2**, 107–114.

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A Randomised Prospective Study Comparing Intravesical Instillations of Mitomycin-C, BCG-Tice, and BCG-RIVM in pTa-pT1 Tumours and Primary Carcinoma *in situ* of the Urinary Bladder

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We compared intravesical instillations with mitomycin-C (MMC), Bacillus Calmette-Guerin (BCG) Tice, and BCG-RIVM in patients with pTa-pT1 papillary carcinoma and primary carcinoma *in situ* (CIS) of the bladder. Nine instillations with MMC were given or 6 weekly instillations with BCG. Early recurrences were treated with additional instillations. For toxicity and efficacy 437 patients were evaluated with a median follow-up of 32 months (range 12–56). Drug-induced and bacterial cystitis were the most frequent side-effects. The number and severity of side-effects (χ^2 test) were comparable in both BCG groups, but were significantly less in the MMC group for drug-induced cystitis ($P = 0.009$), other local side-effects ($P = 0.004$) and systemic side-effects ($P < 0.001$). The disease-free percentage (log-rank test) showed no significant difference for the three arms for papillary tumours ($P = 0.08$), nor the CIS ($P = 0.20$), although for CIS numbers are small. Additional instillations did not influence toxicity or efficacy.
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INTRODUCTION

IN PATIENTS with papillary superficial bladder cancer intravesical instillations have been used as prophylaxis to lower the high recurrence rate after complete transurethral resection (TUR) of a tumour. Both intravesical chemotherapy and intravesical immunotherapy have been used, and are superior to surgery alone in preventing tumour recurrence [1–3]. In patients with carcinoma *in situ* (CIS), complete TUR is difficult. In this case intravesical instillations are used 'therapeutically'. Intravesical chemotherapy in this study utilises mitomycin-C (MMC) because of its proven efficacy with regard to prevention of tumour recurrence and high response rate in patients with CIS [1, 4, 5]. Bacillus Calmette-Guerin (BCG) is the only immunotherapeutic drug that is widely used for superficial bladder cancer. BCG therapy induces an inflammation which consists of immune competent cells reflecting both a humoral and cellular response. However, the exact mechanism of action of BCG remains unknown. In several studies, with a median follow-up of between 12 and 48 months, 63–100% of the patients treated with intravesical BCG for papillary tumours remained disease free [6]. BCG is also effective for the treatment of CIS with complete response rates (negative cystoscopy, cytology and biopsies) of approximately 70% [5, 7–9].

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