patients receiving moderately emetogenic chemotherapy. More patients were withdrawn from the lower-dosage groups (0.25 and 0.5 mg twice daily) due to lack of efficacy, also supporting the 1.0 mg twice daily dose. Of the most frequently reported adverse events, leucopenia, fever and asthenia were recognised side effects of the primary disease and chemotherapy. Headache occurred with similar incidence to that seen in previous granisetron studies.

While the incidence of constipation was higher in this study than in previous studies causality cannot be assessed due to the lack of a comparator. Thus, the results of this study indicate that oral granisetron, at 1.0 mg twice daily, is a safe and effective antiemetic in patients receiving moderately emetogenic chemotherapy. In addition, it offers a convenient dosing regimen.

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. Triozzi PL, Laszlo J. Optimum management of nausea and vomiting in cancer chemotherapy. *Drugs* 1987, **34**, 136-149.
3. Joss RA, Galeazzi RL, Bischoff AK, Pirovino M, Ryssel HJ, Brunner KW. The antiemetic activity of high dose alizapride and high dose metoclopramide in patients receiving cancer chemotherapy: a prospective, randomised, double-blind trial. *Clin Pharmacol Ther* 1986, **39**, 619-624.
4. Sanger GJ. New antiemetic drugs. *Canadian J Physiol Pharmacol* 1990, **68**, 314-324.
5. Andrews PLR, Rapeport WG, Sanger GJ. Neuropharmacology of emesis induced by anti-cancer therapy. *TIPS* 1988, **9**, 334-341.
6. Jones AL, Cunningham D. Management of vomiting associated with cytotoxic therapy. *Br J Hosp Med* 1991, **45**, 85-88.
7. Zambetti M, Bajetta E, Bidoli P, Verusio C. Antiemetic activity of metoclopramide versus alizapride during cancer chemotherapy. *Tumori* 1985, **71**, 609-614.
8. Miner WD, Sanger GJ. Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine M-receptor antagonism. *Br J Pharmacol* 1986, **88**, 497-499.
9. Van Wijngaarden I, Tulp MTM, Soudijn W. The concept of selectivity in 5HT receptor research. *Eur J Pharmacol* 1990, **188**, 301-312.
10. Tonato M, Roila F, Del Favero A. Methodology of antiemetic trials: a review. *Ann Oncology* 1991, **2**, 107-114.
11. Pizzo PA, Young RC. Infections in the cancer patient. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer:Principles and Practice of Oncology*. Philadelphia, Lippincott 1985, pp. 1963-1998.
12. Tabona MV. An overview on the use of granisetron in the treatment of emesis associated with cytostatic chemotherapy. *Eur J Cancer* 1990, **26 (Suppl.1)**, S37-S41.
13. Diehl V, on behalf of the Granisetron Study Group. Fractionated chemotherapy - granisetron or conventional antiemetics? *Eur J Cancer* 1992, **28A** (Suppl.1), S21-S28.

Eur J Cancer, Vol. 28A, Suppl. 1, pp. S32-S35, 1992
Printed in Great Britain

0964-1947/92 $5.00 + 0.00

Are Granisetron and Ondansetron Equivalent in the Clinic?

Stephen Dilly

There are no published direct trials of granisetron vs. ondansetron. Difficulties exist in comparing reported trials because of differences in methodology, especially in response criteria. In this review, a comparison is made between ondansetron and granisetron by recalculating the complete response criterion for granisetron, standardising it against that in the ondansetron programme (i.e. no vomiting). Weighted means have been calculated for three areas of study. Against cisplatin-induced emesis the (weighted) mean percentage of complete responders were calculated at 64% (range 49-77%) for granisetron and 49% (range 40-55%) for ondansetron. Against moderately emetogenic stimuli, the response rates were 76% (range 68-80%) and 73% (range 60-87%) respectively. For fractionated chemotherapy the response rates were 57% and 27% for granisetron and ondansetron respectively. Although not shown by formal statistical analysis, these results suggest that a clinical advantage for granisetron may exist.
Eur J Cancer, Vol. 28A, Suppl.1, pp. S32-S35, 1992.

INTRODUCTION

THE ADVENT of the new 5-HT_3 receptor antagonists has greatly improved the quality of life of patients receiving emetogenic chemotherapy. However, the clinical availability of more than one such 5-HT_3 receptor antagonists leaves the clinician with a choice. To date, there have been no published studies which directly compare the efficacy and safety of granisetron and ondansetron. This presentation aims to compare the efficacy of these two compounds by a review of the published literature to provide an insight into what may be the best way clinically to compare these drugs. Tropisetron, for which relatively little data has been published, has, for this reason, not been considered in this review.

ASSESSMENT OF NAUSEA AND VOMITING

Comparison of the results of clinical trials between ondansetron and granisetron is fraught with difficulty because of differences in the criteria used to assess response rates

Correspondence to: S. Dilly
S. Dilly is at SmithKline Beecham Pharmaceuticals, Watson House, 47-49 London Road, Reigate, Surrey, RH2 9PQ, U.K.

Table 1. Response criteria over the initial 24-h period following chemotherapy

	Granisetron (Soukop 1990 *et al.* [1], Smith 1990 *et al.* [2])	Ondansetron (Hesketh 1989 *et al.* [3], Einhorn 1990 *et al.* [4])
Complete responder	No vomiting* and no or only mild nausea	No emetic episodes**
Major responder	1 episode of vomiting or if no vomiting occurs moderate to severe nausea	1-2 emetic episodes
Minor responder	2-4 vomits regardless of nausea	3-5 emetic episodes
Failure	More than 4 vomits regardless of nausea rating	More than 5 emetic episodes
	Complete responders plus major responders = major efficacy	Complete or major response = success
		Nausea assessed separately as absent, mild, moderate or severe

* Vomit = productive of fluid or dry retch
** Emetic episode = vomit or 1-5 dry retches within a 5-min period

(Table 1). It is the position of SmithKline Beecham in designing the granisetron programme that both vomiting and nausea are important. Nausea has been recognised to be as equally incapacitating as vomiting and to cause much distress to patients [5]. The SmithKline Beecham criteria of efficacy therefore include both nausea and vomiting, so that a complete responder must not vomit nor experience more than mild nausea. Mild nausea is defined as not affecting daily life. In contrast the criterion used in the ondansetron programme for complete responder is simply "no vomiting" allowing the inclusion of patients who may have experienced significant nausea.

COMPARISON OF GRANISETRON AND ONDANSETRON

In order that clinical trials may be compared, the data for granisetron have been re-analysed using the ondansetron criterion of complete response i.e. no vomiting. Whilst the granisetron criteria are more strict, the availability of source data for granisetron and only published data for ondansetron meant that it was only possible to adapt the granisetron data. Three areas of study have been compared; emesis induced by cisplatin, moderately emetogenic chemotherapy and fractionated chemotherapy. The comparison is subject to the caveat that such comparisons only give an indication of where differences may exist. Factors such as the age and sex of the patients and whether they were chemotherapy naive, can influence the incidence of nausea and vomiting and can not be ruled out as a possible source of error. A more complete review of such factors has been carried out by Tonato *et al* [6].

Whilst there is no substitute for direct comparative clinical trials, these remain a major undertaking. The size of the real clinical difference between two treatment groups influences the size of the study necessary to detect this difference. Thus, taking the ondansetron responder rate of ~50% in cisplation patients, to demonstrate a true clinical advantage of 20% for granisetron (i.e. 1 in 5 patients responding to one therapy more than responding to the other) at the 5% significance level and with 80% power, a 186-patient study is required. If the clinical difference was only 10%, and a difference of 1 in 10 patients is clinically relevant, the size of the trial would increase to 776 patients. For a 51% true difference between therapies, a 3130-patient study would be required [7].

RESULTS

Cisplatin-induced emesis

A review of the data for high-dose cisplatin (≥ 50 mg/m^2) encompasses a total of 579 patients receiving ondansetron taken

Table 2. Response rates for granisetron and ondansetron, recalculated with equivalent response criteria. Cisplatin-induced emesis

Granisetron			Ondansetron		
Study	No. of patients	RR%*	Study	No. of patients	RR%*
Soukop *et al.* 1990 [1]	149	62%	Marty *et al.* 1989 [10]	28	46%
Chevallier *et al.* 1990 [8]	114	77%	Hesketh *et al.* 1989 [3]	85	55%
Venner *et al.* 1990 [9]	74	46%	Roila *et al.* 1990 [11]	65	54%
			Marty *et al.* 1990 [12]	76	46%
			DeMulder *et al.* 1990 [13]	95	40%
			Hainsworth *et al.* 1991 [14]	151	40%
			Lebeau *et al.* 1991 [15]	100	66%
TOTAL	214/337	64%	TOTAL	285/579**	49%

* Response rate (RR) for granisetron has been recalculated as "no vomiting"
** Total number of evaluable patients

Table 3. Response rates for granisetron and ondansetron, recalculated with equivalent response criteria. Moderately emetogenic chemotherapy

Granisetron			Ondansetron		
Study	No. of patients	RR%*	Study	No. of patients	RR%*
Smith *et al.* 1990 [2]	223	80%	Marschner *et al.* 1988 [18]	33	73%
Marty *et al.* 1990 [16]	115	74%	Bonneterre *et al.* 1990 [19]	35	66%
Warr *et al.* 1992 [17]	76	70%	Marschner *et al.* 1991 [20]	50	60%
			Kaasa *et al.* 1990 [21]	40	65%
			NCIC 1991 [22]	84	87%
TOTAL	316/414	76%	TOTAL	176/242	73%

* Response rate for (RR) granisetron has been recalculated as "no vomiting"

Table 4. Response rates for granisetron and ondansetron, recalculated with equivalent response criteria. 5-day fractionated chemotherapy

Granisetron			Ondansetron		
Study	No. of patients	RR%*	Study	No. of patients	RR%*
Bremer *et al.* 1992 [23]	103	60%	Burton *et al.* 1990 [25]	82	24%
Diehl *et al.* 1992 [24]	143	55%	Einhorn *et al.* 1990 [4]	35	29%
			Hainsworth *et al.* 1989 [26]	31	35%
TOTAL	140/246	57%	TOTAL	41/148	27%

* Response rate for (RR) granisetron has been recalculated as "no vomiting"

from seven clinical trials and the granisetron data includes 337 patients taken from three clinical trials (Table 2). The range of patients who did not vomit was 49% - 77% for granisetron and 40%-55% for ondansetron. The weighted mean for these figures are 64% and 49% respectively.

Moderately emetogenic chemotherapy

Studies in which patients had received a range of moderately emetogenic chemotherapeutic agents were reviewed (Table 3). Chemotherapy regimens included low-dose cisplatin (>20 - <50mg/m²), cyclophosphamide, fluorouracil, doxorubicin, epirubicin and methotrexate. A total of 414 granisetron-treated patients had an overall "no vomiting" rate of 76%, with a range of 68-80%. The ondansetron data also shows an excellent response rate of 73%, taken from 256 patients, with a range of 60-87%.

Fractionated chemotherapy

Data were reviewed from patients who had received fractionated chemotherapy regimens including the following agents; cisplatin, etoposide and ifosfamide.

Two granisetron studies including a total of 246 patients, and three ondansetron studies including 148 patients, showed overall "no vomiting" rates of 57% (range 55-60%) and 27% (range 24-35%) respectively, (Table 4).

DISCUSSION

Whilst there is no substitute for direct head-to-head trials, this review has suggested some areas that are worth examining in terms of documenting whether or not a real clinical difference exists between granisetron and ondansetron. Although not shown by formal statistical analysis, the results of this comparison suggest a 15% difference between the two agents in the control of cisplatin-induced emesis and a 30% difference in the control of emesis induced by fractionated chemotherapy in favour of granisetron. Taken together with granisetron's simple dosage regimen this may indicate a meaningful clinical advantage of granisetron over ondansetron. The next step is to carry out comparative trials with granisetron and ondansetron to investigate these issues properly. The importance of clinical trials with sufficient statistical power, and therefore adequate patient numbers, has been highlighted. These trials are currently under way.

1. Soukop M on behalf of the Granisetron Study Group. A comparison of two dose levels of granisetron in patients receiving high-dose cisplatin. *Eur J Cancer* 1990, **26**(Suppl 1), S15-S19.
2. Smith IE on behalf of the Granisetron Study Group. A comparison of two dose levels of granisetron in patients receiving moderately emetogenic cytostatic chemotherapy. *Eur J Cancer* 1990, **26**(Suppl 1), S19-S23.
3. Hesketh PJ, Murphy WK, Lester EP *et al.* GR 38032F (GR-C507/75): A novel compound effective in the prevention of acute

cisplatin-induced emesis. *J Clin Oncol* 1989, **7**, 700-705.
4. Einhorn LH, Nagy C, Werner K, Finn AL. Ondansetron: A new antiemetic for patients receiving cisplatin chemotherapy. *J Clin Oncol* 1990, **8**, 731-735.
5. Coates A, Abraham S, Kaye SB *et al.* On the receiving end-patient perception of the side effects of cancer chemotherapy. *Eur J Can Clin Oncol* 1983, **19**, 203-208.
6. Tonato M, Roila F, Delfavero A. Methodology of antiemetic trials: A review. *Annals Oncology* 1991, **2**, 107-114.
7. Machin D, Campbell MJ. Statistical tables for the design of clinical trials. Blackwell Scientific Publications 1987.
8. 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.
9. Venner P. Granisetron for high-dose cisplatin (HDCP) induced emesis: A randomised double-blind study. *Proceedings of ASCO* 1990, **9**, 320 Abst. no 1238.
10. Marty M, Droz JP, Pouillart P, Paule B, Brion N, Bons J. GR 38032F, a 5-HT_3 receptor antagonist, in the prophylaxis of acute cisplatin-induced nausea and vomiting. *Cancer Chemother Pharmacol* 1989, **23**, 389-391.
11. Roila F, Bracarda S, Tonato M *et al.* Ondansetron (GR 38032) in the prophylaxis of acute and delayed cisplatin-induced emesis. *J Clin Oncol* 1990, **2**, 268-272.
12. Marty M, Pouillart P, Scholl S *et al.* Comparison of the 5-hydroxytryptamine$_3$ (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 1990, **322**, 816-821.
13. De Mulder PHM, Seynaeve C, Vermorken JB *et al.* Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. *Ann Intern Med* 1990, **113**, 834-840.
14. Hainsworth J, Harvey W, Pendergrass K *et al.* A single-blind comparison of intravenous ondansetron, a selective serotonin antagonist, with intravenous metoclopramide in the prevention of nausea and vomiting associated with high-dose cisplatin chemotherapy. *J Clin Oncol* 1991, **9**, 721-728.
15. Lebeau B, Depierre A, Allens H(d') and the French Pneumology Group for the Ondansetron Study. Comparison of ondansetron with or combined regimen of alizapride and methylprednisolone in the prophylaxis of cisplatin-induced emesis in patients with lung cancer. (In French) *Sem Hôp Paris* 1991, **67**, 1350-1357.
16. Marty M on behalf of the Granisetron Study Group. A comparative study of the use of granisetron, a selective 5-HT_3 antagonist, vs a standard antiemetic regimen of chlorpromazine plus dexamethasone in the treatment of cytostatic-induced emesis. *Eur J Cancer* 1990, **26**(Suppl 1), S28-S32.
17. Warr D, Willan A, Fine S *et al.* Superiority of granisetron to dexamethasone plus prochlorperazine in the prevention of chemotherapy induced emesis. *J Natl Cancer Inst* 1991, **83**, 1169-1173.
18. Marschner N, Nagel G, Bruntsch U *et al.* Oral GR 38032F as antiemetic prophylaxis in patients receiving cyclophosphamide containing chemotherapy regimens (abst.) *Proc Eur Soc Med Oncol* 1988 Abst. 266.
19. Bonneterre J, Chevallier B, Metz R *et al.* A randomised double-blind comparison of ondansetron and metoclopramide in the prophylaxis of emesis induced by cyclophosphamide, fluorouracil and doxorubicin or epirubicin chemotherapy. *J Clin Oncol* 1990, **8**, 1063-1069.
20. Marschner N, Adler M, Nagel GA *et al.* Double-blind randomised trial of the antiemetic efficacy and safety of ondansetron and metoclopramide in advanced breast cancer patients treated with epirubicin and cyclophosphamide. *Eur J Cancer* 1991, **27**, 1137-1140.
21. Kaasa S, Kvaloy S, Dicato MA *et al.* A comparison of ondansetron with metoclopramide in the prophylaxis of chemotherapy-induced nausea and vomiting: a randomised, double-blind study. *Eur J Cancer* 1990, **26**, 311-314.
22. NCIC Clinical Trials Group. An assessment of the antiemetic efficacy, tolerance and safety of GR 38032F vs dexamethasone plus metoclopramide in patients with breast cancer receiving "CMF" chemotherapy. *Proc Nat Cancer Inst Canada*, Toronto, Spring 1991 333-349.
23. Bremer K. A single-blind comparative study of the efficacy of intravenous granisetron compared with alizapride plus dexamethasone in the prophylaxis and control of emesis in patients receiving cytostatic therapy over a 5-day treatment period. *Eur J Cancer* 1992 (In press).
24. Diehl V on behalf of the Granisetron Study Group. Fractionated chemotherapy - granisetron or conventional antiemetics? *Eur J Cancer* 1992, **28A**(Suppl 1), S21-S28.
25. Burton G, Huang A, Lazarus H *et al.* A double-blind randomised comparison of three doses of i.v. ondansetron for the prevention of emesis induced by multiday cisplatin therapy (abst.) *Proc Am Soc Clin Oncol* 1990, **9**, 1269.
26. Hainsworth JD, Omura GA, Khojasteh A *et al.* GR 38032F: A new antiemetic effective in a multiple day regimen of cisplatin (DDP) chemotherapy (abst.) *Proc Am Soc Clin Oncol* 1989, **8**, 328.