

Granisetron vs ondansetron: is it a question of duration of 5-HT₃ receptor blockade?

P Blower*¹ and M Aapro²

¹Poole House, Great Yeldham, Halstead, Essex CO9 4HP, UK; ²Clinique de Genolier, 1272, Genolier, Switzerland

DOI: 10.1038/sj/bjc/6600313 www.bjcancer.com

© 2002 Cancer Research UK

Sir

We read with interest the publication by de Wit *et al* (2001) that there may be effective cross-over to granisetron after failure on ondansetron; both are selective 5-HT₃ receptor antagonists, a class of drugs considered the 'gold-standard' antiemetic agents for the control of emesis in cancer patients undergoing chemo- and radiotherapy. While we support the outcome that granisetron demonstrates superior efficacy to ondansetron, an effect that has been previously reported by Terrey and Aapro (1996), we have some concerns about the study design and the authors' interpretation of the results.

Firstly, from the outset this study favours granisetron. We recognise that the trial of de Wit *et al* (2001) involved only a small number of patients ($n=40$), however, for the study to be a balanced cross-over design, patients should have been selected from a background of failure on both ondansetron and granisetron with previous chemotherapy cycles. Moreover, the authors fail to discuss the possibility of a psychological bias toward the introduction of the 'new' drug. Psychological factors can influence treatment success and are known to be associated with anticipatory nausea and vomiting, a negative phenomenon that can have potentially disabling effects on patients undergoing successive chemotherapy cycles. Conversely, there may be positive psychological elements benefiting the patient – the design of this trial does not control for this effect. In double-blind trials in which patients fail on one antiemetic treatment and then go on to receive the antiemetic in subsequent cycles, anticipation of a switch in therapy may be enough to demonstrate an improved response.

Despite its importance to the interpretation of the study results, de Wit *et al* (2001) have made no reference to the longer duration of action of granisetron *vs* ondansetron, nor the pharmacodynamic properties of the two agents. Compelling data accumulated from cutaneous flare experiments in human volunteers demonstrate that, following a single infusion of granisetron, 40 $\mu\text{g kg}^{-1}$, the 5-HT₃ receptor-mediated axon flare reflex is significantly reduced for at least 24 h (Cooper *et al*, 1988; Upward *et al*, 1990). This contrasts with a 2.6-fold shorter duration of action after infusion with ondansetron, 8 and 16 mg (Sweetland *et al*, 1992) and is further supported by the longer plasma half-life of granisetron (about 10 h; Carmichael *et al*, 1989) compared with ondansetron (about 3.8 h; Roila and Del Favero, 1995). Furthermore, granisetron

differs from the competitive antagonist ondansetron in that it displays insurmountable antagonism at vagal afferent 5-HT₃ receptors (Newberry *et al*, 1993), and it is this property that is thought to underlie the phenomenon that its pharmacodynamic half-life far exceeds its plasma half-life.

The authors fail to acknowledge further important data in their discussion. The two chemotherapeutic agents administered in this study, cisplatin ($\geq 50 \text{ mg m}^{-2}$) and cyclophosphamide ($\geq 500 \text{ mg m}^{-2}$), differ in their emetogenic potential as well as the time of onset of their emetic action (Doherty, 1999) (Table 1). While de Wit *et al* (2001) report complete protection following cisplatin-based chemotherapy in two out of seven patients receiving granisetron and none out of six patients receiving ondansetron, the principal difference between the efficacy of ondansetron and granisetron in this study was following cyclophosphamide-based therapy. Fifty-eight per cent of patients receiving cyclophosphamide experienced complete protection of emesis following a single dose of granisetron, compared with 7% following a single dose of ondansetron; the later onset of emesis following cyclophosphamide must favour the longer duration of antiemetic effect of granisetron.

Additionally, de Wit *et al* (2001) state that, 'there are no data to support the use of higher doses of the same 5-HT₃ receptor antagonists in patients failing the recommended dosage,' citing Gandara *et al* (1998). However, a dose-related response ($P < 0.001$) for oral dolasetron has been shown between doses of 25 and 200 mg (complete response rates 60.5 and 76.3% for 100 and 200 mg dolasetron, respectively; Fauser *et al*, 1996), despite a recommended dosage for the agent of 100 mg. Similar dose-related effects have also been reported with ondansetron. For example, a Phase I study comparing three doses of intravenous ondansetron t.d.s. (0.015, 0.15 and 0.3 mg kg^{-1}) indicated a trend towards increased efficacy with higher doses (complete response rates were 15, 46 and 58% respectively), though only

Table 1 Emetogenic potential and onset of emetic response following administration of cisplatin and cyclophosphamide

	Emetogenic potential	Onset of emetic response
Cisplatin $\geq 50 \text{ mg m}^{-2}$	High >90%	1.5–3 h
Cyclophosphamide $\geq 500 \text{ mg m}^{-2}$	Moderate 30–60%	9–12 h

*Correspondence: P Blower;
E-mail: peter@rblower.freeserve.co.uk

the 0.015 mg kg⁻¹ dose was shown to be significantly different from the other dose levels (Grunberg, 1992). Further studies have reported significantly superior efficacy with a single dose on ondansetron, 32 mg, compared with a single 8 mg dose (Beck *et al*, 1992; Tsavaris *et al*, 2001). Moreover, studies comparing granisetron, 40 and 160 µg kg⁻¹, show a trend towards increased efficacy at the higher dose (Smith, 1993; Soukop, 1994); 24 h after administration of chemotherapeutic agents, 81% of granisetron, 160 mcg kg⁻¹, were emesis-free compared with 75% receiving granisetron 40 µg kg⁻¹ (Smith, 1993). In addition, patients refrac-

tory to other 5-HT₃ receptor antagonists have been shown to respond well to granisetron, at doses that are higher than generally used, in subsequent chemotherapy cycles (Carmichael *et al*, 1998).

In conclusion, the effective 'switch' to granisetron in this study may, therefore, be due to a number of factors, but is likely to be attributable primarily to the longer duration of action of granisetron compared with ondansetron rather than the lack of cross resistance between 5-HT₃ receptor antagonists.

REFERENCES

- Beck TM, Hesketh PJ, Madajewicz S, Navari RM, Pendergrass K, Lester EP, Kish JA, Murphy WK, Hainsworth JD, Gandara DR (1992) Stratified, randomized, double-blind comparison of intravenous ondansetron administered as a multiple-dose regimen versus two single-dose regimens in the prevention of cisplatin-induced nausea and vomiting. *J Clin Oncol* **10**(12): 1969–1975
- Carmichael J, Cantwell BMJ, Edwards CM, Zussman BD, Thompson S, Rapeport WG, Harris AL (1989) A pharmacokinetic study of granisetron (BRL 43694A), a selective 5-HT₃ receptor antagonist: correlation with antiemetic response. *Cancer Chemother Pharmacol* **24**: 45–59
- Carmichael J, Keizer HJ, Cupissol D, Milliez J, Scheidel P, Schindler AE (1998) Use of granisetron in patients refractory to previous treatment with antiemetics. *Anti-Cancer Drugs* **9**: 381–385
- Cooper SM, Arnold BDC, Rapeport WG (1988) Inhibition of 5-HT induced axon-reflex flares by BRL 43694, a novel 5-HT₃ receptor antagonist. *Br J Clin Pharmacol* **25**: 106P–107P
- de Wit R, de Boer AC, Linden GHM, Stoter G, Sparreboom A, Verweij J (2001) Effective cross-over to granisetron after failure to ondansetron, a randomized double blind study in patients failing ondansetron plus dexamethasone during the first 24 hours following highly emetogenic chemotherapy. *Br J Cancer* **85**: 1099–1101
- Doherty KM (1999) Closing the gap in prophylactic antiemetic therapy: patient factors in calculating the emetogenic potential of chemotherapy. *Clin J Oncol Nurs* **3**: 113–119
- Fausser AA, Duclos B, Chemaissani A, Del Favero A, Cognetti F, Diaz-Rubio E, Funes H, Conte PF, Dressler H (1996) Therapeutic equivalence of single oral doses of dolasetron mesilate and multiple doses of ondansetron for the prevention of emesis after moderately emetogenic chemotherapy. European Dolasetron Comparative Study Group. *Eur J Cancer* **32A**: 1523–1529
- Gandara DR, Roila F, Warr D, Edelman MJ, Perez EA, Gralla RJ (1998) Consensus proposal for 5-HT₃ antagonists in the prevention of acute emesis related to highly emetogenic chemotherapy. Dose, schedule, and route of administration. *Support Care Cancer* **6**: 237–243
- Grunberg SM (1992) Phase I and other dose-ranging studies of ondansetron. *Semin Oncol* **19**: 16–22
- Newberry NR, Watkins CJ, Sprosen TS, Blackburn TP, Grahame-Smith DG, Leslie RA (1993) BRL 46470 potently antagonizes neural responses activated by 5-HT₃ receptors. *Neuropharmacology* **32**: 729–735
- Roila F, Del Favero A (1995) Ondansetron clinical pharmacokinetics. *Clin Pharmacokinet* **29**: 95–109
- Smith IE (1993) A dose-finding study of granisetron, a novel antiemetic, in patients receiving cytostatic chemotherapy. *J Cancer Res Clin Oncol* **119**: 350–354
- Soukop M (1994) A dose-finding study of granisetron, a novel antiemetic, in patients receiving high-dose cisplatin. *Support Care Cancer* **2**: 177–183
- Sweetland J, Lettis S, Fowler PA, Thomas M (1992) Duration of the inhibitory effect of intravenous ondansetron on intradermal 5-HT-induced flare. *Br J Clin Pharmacol* **33**: 565P
- Terrey J-P, Aapro MS (1996) The activity of granisetron in patients who had previously failed ondansetron antiemetic therapy. *Eur J Clin Res* **8**: 281–288
- Tsavaris N, Kosmas CH, Vadiaka M, Kontos A, Katsorida M, Dimitrakopoulos A, Zerai A, Koufos CH (2001) Efficacy of ondansetron treatment for acute emesis with different dosing schedules 8 vs 32 mg. A randomized study. *J Exp Clin Cancer Res* **20**(1): 29–34
- Upward JW, Arnold BDC, Link C, Pierce DM, Allen A, Tasker TCG (1990) The clinical pharmacology of granisetron (BRL 43694), a novel specific 5-HT₃ antagonist. *Eur J Cancer* **26**(suppl 1): S12–S15