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Assessing the benefits of anti-emetic innovation

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This paper reviews recent anti-emetic developments, with particular reference to the 5-HT_3 receptor antagonists. These drugs are at least as effective as conventional regimens for controlling acute nausea and vomiting in patients receiving highly or moderately emetogenic chemotherapy and abdominal radiotherapy. They have less side effects than do alternative drugs. Improved control of acute nausea and vomiting by 5-HT_3 receptor antagonists seems to reduce anticipatory symptoms in subsequent cycles. Dexamethasone enhances activity of 5-HT_3 receptor antagonists in highly emetogenic chemotherapy. Improved control of acute nausea and vomiting by 5-HT_3 receptor antagonists may remove one obstacle to offering palliative chemotherapy.

Key words: 5-HT_3 receptor antagonists, dexamethasone, granisetron, metoclopramide, nausea, ondansetron, vomiting.

Introduction

In a study by Coates *et al.*[1] questionnaires were sent to patients to assess the impact of chemotherapy on their lives. The patients ranked vomiting and nausea as the most distressing effects of chemotherapy. Many believe that nausea, because it is often prolonged, may actually be more distressing than vomiting. It is of course much more difficult to measure. This paper reviews recent anti-emetic developments, with particular reference to the 5-HT_3 receptor antagonists.

Clinical benefits from improved emesis control

The most obvious improvement from better control of nausea and vomiting is enhanced quality of life of patients undergoing cancer treatment. This may mean less hospitalization, particularly if the anti-emetic regimen is easy to administer. In addition, the barriers to offering and accepting treatment may be removed. If fewer patients withdraw from potentially curative chemotherapy, survival rates should improve. A substantially greater number of patients may benefit from palliative treatment opportunities opened up by better control of nausea and vomiting.

The 5-HT_3 receptor antagonists offer the prospect of an improved therapeutic ratio in the control of nausea and vomiting induced by chemotherapy and radiotherapy. Unfortunately, the advantage of these drugs over conventional agents seems largely confined to the control of acute emesis. Joss and Dott[2] (Table 1) have recently compared the efficacy of granisetron with high-dose metoclopramide plus dexamethasone in patients receiving high-dose cisplatin. Granisetron gave a higher incidence of major protection against emesis than did the combination. This was accompanied by a lower incidence of adverse effects — in particular a lower incidence of extrapyramidal side effects. Granisetron was also superior to chlorpromazine plus dexamethasone in patients receiving moderately emetogenic chemotherapy. The only consistent side effects from granisetron were headache (14%) and constipation (4%).

Granisetron has also been shown to be highly effective in controlling radiation-induced emesis. In an open study of 32 patients, a single intravenous dose of granisetron completely protected 56% of patients from nausea and vomiting induced by total body irradiation (7.5 Gy).[3] An earlier study by

Table 1. Efficacy and adverse events of granisetron compared with standard anti-emetic regimens

Chemotherapy	Anti-emetic regimen	Effect
High-dose cisplatin	granisetron	83% major protection
	high-dose metoclopramide + dexamethasone	77% major protection
	granisetron	23% adverse events[a]
	high-dose metoclopramide + dexamethasone	33% adverse events
Moderately emetogenic chemotherapy	granisetron	70% complete response
	chlorpromazine + dexamethasone	50% complete response

[a] The only consistent side effects from granisetron were headache (14%) and constipation (4%).
Reproduced from reference 2.

Priestman,[4] using ondansetron (8 mg three times/day), demonstrated excellent acute anti-emetic control in patients receiving radiotherapy (8–10 Gy) to the upper abdomen, compared with metoclopramide. However, on days 2 and 3 this control was not sustained and fell rapidly to the same level obtained with the conventional drug.

The addition of dexamethasone to 5-HT_3 receptor antagonists increases their efficacy. In a crossover study by Smith *et al.*,[5] in which the steroid was added to ondansetron, anti-emetic control was considerably enhanced by the combination, which was preferred by the majority of patients.

Jones *et al.*[6] compared ondansetron and dexamethasone as single agents in patients receiving moderately emetogenic chemotherapy. The two drugs, both given for 5 days, were seen to be very comparable in control of acute emesis. Dexamethasone, however, was found to be superior to ondansetron in the control of delayed nausea. Further evidence for the lack of efficacy of 5-HT_3 receptor antagonists in delayed emesis was obtained from a study by Kris *et al.*[7] using high-dose oral ondansetron (16 mg three times/day) in patients receiving cisplatin. Acute emesis was initially controlled in most patients with the use of high-dose metoclopramide, dexamethasone and lorazepam, but over the following 4 days patients were switched to ondansetron and complete control of delayed emesis was observed in only 15% of patients.

The relative efficacies of the different 5-HT_3 receptor antagonists are not known. There have been indirect retrospective comparisons made between them, but it is difficult to draw conclusions from studies employing different chemotherapy and anti-emetic comparatory regimens and different response criteria. It will be necessary to wait for the results of direct comparisons of 5-HT_3 receptor antagonists before any reliable conclusions can be drawn concerning their relative efficacies. Preliminary evidence suggests a patient preference for granisetron.[8]

Anticipatory nausea and vomiting can be a most troublesome experience for a minority of patients receiving chemotherapy. Some studies[9] have suggested that anticipatory nausea and vomiting occurs in approximately 10% of patients; others have reported even higher figures. Better control of acute nausea and vomiting reduces subsequent anticipatory symptoms. Aapro *et al.*[10] concluded that granisetron had contributed to the reduction of anticipatory nausea and vomiting, which was found to occur in less than 4% of the study group. No nausea or vomiting were observed prior to chemotherapy in patients who had received more than seven treatment cycles.

Open questions

The extent to which study findings are applicable to unselected patients is also not known. Most anti-emetic trials have strict exclusion criteria and, as a consequence, many of the conclusions may not be applicable to unselected, routine patient populations.

Another question that remains to be answered is whether steroids enhance the anti-emetic efficacy of 5-HT_3 receptor antagonists in patients receiving moderately emetogenic chemotherapy. It would be surprising if they did not, since the combination is superior with highly emetogenic regimens, but as yet, there are no firm data available. Approximately 80% of publications involving 5-HT_3 receptor antagonists relate to highly emetogenic chemotherapy and only 20% to moderately emetogenic chemotherapy. This is in conflict with the distribution of chemotherapy in routine clinical practice, as exemplified recently by Jones *et al.*[11] who assumed that approximately 75% of their patients were receiving moderately emetogenic chemotherapy, with only 10% receiving highly emetogenic regimens. The relative efficacy of the 5-HT_3 receptor antagonists compared with regimens of alternative drug(s) plus steroid started the day before the administration of chemotherapy, is also unknown. Williams *et al.*[12] showed that administering domperidone and dexamethasone the day before chemotherapy gave more effective prevention of emesis than the same combination starting on the day of chemotherapy. The timing and duration of the addition of dexamethasone to anti-emetic regimens may be important in the control of acute and delayed nausea and vomiting.

A further aspect of the control of nausea and vomiting that should not be ignored is the progressive decline in the control of nausea and vomiting with successive courses of chemotherapy. There is a noteworthy paucity of evidence on the ability of newer anti-emetic regimens to maintain control of nausea and vomiting, but Blijham and colleagues[13] documented that efficacy could be maintained over a number of cycles in most patients receiving granisetron with moderately or severely emetogenic chemotherapy, although some fall-off occurred with patients receiving high-dose cisplatin.

Table 2. Author's view of 100 European patients (all ages) with advanced solid tumors

At present:	
20 patients are given palliative cytotoxic chemotherapy (mostly moderately emetogenic)	
Reasons why 80 patients are not given chemotherapy:	
efficacy extremely low	15%
social disruption	20%
risk of nausea/vomiting	30%
risk of alopecia	15%
other specific side effects	10%
non-specific physical/psychological toxicity	10%
If anti-emetic innovation reduces nausea/vomiting:	
— by a third, eight more patients might be offered palliative chemotherapy, an increase of 40%.	
— by half, 12 more patients might be offered palliative chemotherapy, an increase of 60%.	

Conclusions

A current gold-standard regimen for the prevention of nausea and vomiting in patients receiving severely or moderately emetogenic chemotherapy can be envisaged. On the basis of the data available this could comprise a 5-HT_3 receptor antagonist, together with a steroid, administered on the day before chemotherapy and continued for several days for the prevention of delayed emesis.

Better control of nausea and vomiting may remove one of the obstacles to offering palliative cytotoxic chemotherapy. Speculative data are given in Table 2. It is suggested that the risk of nausea and vomiting could account for 30% of patients with advanced solid tumors not being offered chemotherapy. Improvements in emetic control might be expected to result in increases in the number of patients offered chemotherapy. While these figures are speculative, the possibility of such an effect should be borne in mind in any thorough cost-benefit analysis.

References

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**: 203–8.
2. Joss RA, Dott CS on behalf of the Granisetron Study Group. Clinical studies with granisetron, a new 5-HT_3 receptor antagonist for the treatment of cancer chemotherapy-induced emesis. *Eur J Cancer* 1993; **29A (Suppl 1)**: S22-9.
3. Hunter AE, Prentice HG, Pothecary K, *et al.* Granisetron, a selective 5-HT_3 receptor antagonist, for the prevention of radiation induced emesis during total body irradiation. *Bone Marrow Transplant* 1991; **7**: 439–41.
4. Priestman TJ. Clinical studies with ondansetron in the control of radiation-induced emesis. *Eur J Cancer Clin Oncol* 1989; **25 (Suppl 1)**: S29–33.
5. Smith DB, Newlands ES, Rustin GJS, *et al.* Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containing chemotherapy. *Lancet* 1991; **338**: 487–90.
6. 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**: 483–7.
7. Kris MG, Tyson LB, Clark RA, *et al.* Oral ondansetron for the control of delayed emesis after cisplatin. *Cancer* 1992; **70**: 1012–6.
8. Jantumen JT, Muhonen TT, Kataja VV, *et al.* 5-HT_3 receptor antagonists in the prophylaxis of acute vomiting induced by moderately-emetogenic chemotherapy — a randomised study. *Eur J Cancer* 1993; **29A**: 1669-72.
9. Aapro MS, Kirchner V, Teney JP. The impact of granisetron on anticipatory nausea and vomiting. *Br J Cancer* 1994, in press.
10. Aapro MS, Kirchner V, Terrey J-P. Is anticipatory nausea and vomiting a thing of the past? *Proc Am Soc Clin Oncol* 1992; **11**: 394 (Abstract).
11. Jones AL, Lee GJ, Bosanquet N. The budgetary impact of 5-HT_3 receptor antagonists in the management of chemotherapy-induced emesis. *Eur J Cancer* 1993; **29A**: 51–6.
12. Williams CJ, Davies C, Raval M, *et al.* Comparison of starting antiemetic treatment 24 hours before or concurrently with cytotoxic chemotherapy. *Br Med J* 1989; **298**: 430–1.
13. Blijham GH on behalf of the Granisetron Study Group. Does granisetron remain effective over multiple cycles? *Eur J Cancer* 1992; **28A (Suppl 1)**: S17–21.

Appendix—Discussion

MS Aapro (Switzerland): This presentation has shown that there is a benefit from treatment with 5-HT_3 receptor antagonists. However, these compounds should possibly not be used in chemotherapy which has low emetogenic potential, as demonstrated in the study by Jones *et al.*[1] or for delayed emesis, until there is further evidence to support their use.

J Carmichael (UK): With respect to delayed vomiting, there are two separate scenarios; high-dose cisplatin with delayed emesis on days 2–7, and delayed emesis following split-dose chemotherapy where 5-day schedules are used. What is your opinion of the use of 5-HT_3 receptor antagonists in a split-dose chemotherapy schedule?

G Rees (UK): There are not enough data available to answer this question. However, the data that we do have are not very encouraging for the use of these drugs in delayed nausea and vomiting in any setting.

G Rustin (UK): I would like to add a word of caution. The use of dexamethasone is increasing especially in split-dose chemotherapy and we have now started to administer dexamethasone the day before chemotherapy, continue for 5 days during the treatment and perhaps for another 5 days afterwards to counteract late emesis. Only 2 weeks after we published our paper in the *Lancet* on dexamethasone *vs* ondansetron,[2] we published a letter of two cases of *Pneumocystis carinii* pneumonia with choriocarcinoma in patients.[3] We have used exactly the same chemotherapy regimen for about 12 years, and up to the introduction of ondansetron/dexamethasone we had never seen such a case. Dexamethasone is very immunosuppressive and caution might be advisable.

G Rees (UK): The dose and duration of dexamethasone therapy needs careful consideration. Weight gain and cushingoid side effects can be a problem with both prolonged and high-dosage schedules, and quite a few patients report sleep disturbances when on dexamethasone. I believe that Jones *et al.*[1] used a discontinuing dosage: 8 mg was given initially, and then the dose was decreased from 4 mg four times/day to 1 mg four times/day over days 1–5.

R Herrmann (Switzerland): I would like to add another word of caution. Cell culture studies have shown that dexamethasone actually promotes growth of human malignant tumors in cell culture. To administer dexamethasone to all patients is possibly inadvisable, and the effect of dexamethasone on tumor growth should be considered.

M Aapro (Switzerland): Studies have also shown that steroids do not modify the efficacy of chemotherapy *in vitro*.[4] They have been shown to enhance growth of especially fresh human tumor samples *in vitro*,[5] but whether this is a direct tumor enhancing effect, or whether it is an effect to ablate some of the cytotoxic or cytostatic effects of the *in vitro* system is debatable. However, there are some cell lines which are steroid responsive, particularly some hematopoietic cell lines. On the other hand, we know that other cell lines are destroyed by steroids. In breast cancer, many clinical studies using relatively low-dose prednisone have shown no negative effects and, in fact, the addition of prednisone has showed a possible improvement in survival of patients at least in adjuvant studies. Certainly steroids cannot be used as if they were miracle drugs without any side effects. They are potent drugs which can have long-term side effects. The correct dosage of steroids is unknown, but it is evident that relatively high doses of dexamethasone are used when perhaps they are not necessary. The minimally effective dose of steroids to potentiate antiemetics should be studied.

References

1. 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**: 483–7.
2. Smith DB, Newlands ES, Rustin GJS, *et al.* Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containing chemotherapy. *Lancet* 1991; **338**: 487–90.
3. Rustin GJS, Smith DB, Newlands S. *Pneumocystis carinii* pneumonia and high dose dexamethasone to prevent emesis of chemotherapy. *Lancet* 1991; **338**: 946.
4. Aapro MS, Serokiman R, Alberts DS. Lack of dexamethasone effect on the antitumor activity of cisplatin. *Cancer Treat Rep* 1983; **67**: 1013–17.
5. Eliason JF, Aapro MS, Decrey D, *et al.* Non-linearity of colony formation by human tumour cells from biopsy samples. *Br J Cancer* 1985; **52**: 311-18.