Eur J Cancer Clin Oncol, Vol. 21, No. 2, pp. 155–157, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

Perspectives and Commentaries

Antiemetic Treatment

RICHARD J. GRALLA
Memorial Sloan-Kettering Cancer Centre, 1275 York Avenue, New York, NY 10021, U.S.A.

(A COMMENT ON: Cognetti F, Pinnarò P, Carlini P, Conti EM. Cortese M, Pollera CF. Randomized open cross-over trial between metoclopramide (MCP) and dexamethazone (DXM) for the prevention of cisplatin-induced nausea and vomiting. *Eur J Cancer Clin Oncol* 1984, **20**, 183–187.)

OPTIMAL control of emesis in patient receiving cancer chemotherapy remains an important objective in supportive care. Studies over the past few years have helped to identify useful agents, establish proper trial design and indicate directions for further improvement. These comments will try to summarize briefly current progress in antiemetic therapy.

Recent trials have examined a variety of agents, representing several different classes of drugs. These include phenothiazines, cannabinoids, substituted benzamides, butyrophenones and corticosteroids. Additionally, other types of agents (such as anticholinergics and benzodiazepines) have been studied but not in as great a depth as those listed above. Careful trials yielding quantitative results with single antiemetic agents are necessary to establish the efficacy of available drugs, to outline side-effects and to help determine a rational basis for the use of appropriate agents in combination.

Table 1 outlines the results of random-assignment trials in which frequently used antiemetics have been compared with each other and with placebo. In most instances other agents from the same classes of drugs have also been studied. In addition to the random-assignment trials of Table 1, several open phase II studies supporting the use of these agents have also been conducted. Review articles detailing trials with cannabinoids [1], metoclopramide [2] and phenothiazines [3] were published in 1983.

As seen in Table 1, four of the five agents have been compared with placebo, and in each case the study agent was found to be superior [4–9]. Although dosages, schedules and routes of administration vary among the trials, certain patterns have emerged. THC by oral administration [10, 11] and prochlorperazine (oral or intramuscular) appear to be less useful when given with chemotherapeutic agents most likely to produce emesis, such as cisplatin. Metoclopramide, haloperidol [12, 13] and dexamethasone [14, 15] have all shown useful results as antiemetics in patients receiving cisplatin.

The identification of active single agents gives the necessary information to proceed rationally with studies combining antiemetics. Guidelines for the design of combination regimens should include: (1) the use of active single drugs employing the best doses, routes of administration and schedules as determined in prior trials; (2) regimens should minimize the combination of agents with overlapping toxicities; and (3) agents should not have opposing pharmacologic properties.

Pharmacokinetic studies can be helpful in determining the proper dosage of the single antiemetic agents. As an example, a recent trial has reported that a peak blood level of >840 ng/ml of metoclopramide is associated with improved therapeutic results [16]. Additionally, as clinical experience has been gained with this agent in high intravenous doses, it has become apparent that younger patients (below age 30) are at greater risk for acute dystonic reactions, and that this toxicity can often be prevented or easily treated by the use of diphenhydramine [17].

The most effective regimens reported to date have included combinations adding corticosteroids to metoclopramide [18–20] or to butyrophenones [21].

Accepted 8 June 1984.

Table 1. Antiemetic random-assignment trials comparing single agents

Versus	Prochlorperazine* (p.o. or i.m.)	THC† (p.o.)	Metoclopramide‡ (i.v.—high dose)	Haloperidol§ (p.o. or i.v.)	Dexamethasone‖ (p.o. or i.v.)
Placebo	prochlorperazine superior[3,5]	THC superior[2,3,5]	Metoclopramide superior[1]		dexamethasone superior[4]
Prochlorperazine (p.o. or i.m.)	—	THC superior or equivalent[3,5]	metoclopramide superior[1]		
THC (p.o.)	THC superior or equivalent[3,5]	—	metoclopramide superior[1]	equivalent, but less toxicity with haloperiodol[5]	
Metoclopramide (i.v.—high dose)	metoclopramide superior[1]	metoclopramide superior[1]	—	metoclopramide superior, but both effective[1]	metoclopramide superior or equivalent[1]
Haloperidol (p.o. or i.v.)		equivalant, but less toxicity with haloperidol[5]	metoclopramide superior, but both effective[1]	—	
Dexamethasone (p.o. or i.v.)			metoclopramide superior or equivalent[1]		—
References	4, 5, 10	4, 5, 6, 10–12	7, 8, 11, 13–15	12, 13	9, 14, 15

*Chemotherapeutic agent: cisplatin.
†Chemotherapeutic agent: methotrexate.
‡Chemotherapeutic agents: nitrosourea + 5-FU.
§Chemotherapeutic agents: cyclophosphamide + methotrexate + 5-FU.
‖Chemotherapeutic agents: various.

The combination currently being investigated at our institution combines metoclopramide (2 mg/kg × three doses, or 3 mg/kg × two doses i.v.) with dexamethasone (20 mg i.v. given once, 30 min before chemotherapy) and diphenhydramine (50 mg i.v. at the time of the dexamethasone). The diphenhydramine is given prophylactically to lessen the chance of dystonic reactions. To date, this combination has allowed a shorter course of antiemetic treatment, with fewer side-effects and a trend toward improved efficacy [20, 22].

With the increased number of antiemetic studies over the past 4–5 yr has come the realization that such trials are not easy to conduct. To obtain objective results close patient observation is needed; this is time-consuming and not all centers have the necessary personnel to devote their full attention to such activities. While subjective data and patient questionnaires may be useful, these instruments have yet to be compared with objective data or with observer-generated results. Additionally, many of the antiemetic agents can alter perception or memory, and the ability of the patient to give accurate quantitative data must be questioned.

Important factors that should be considered in study design include: (1) standardization of the patient population, indicating whether or not patients have previously received chemotherapy (and may therefore have anticipatory emesis); (2) standardization of the emetic stimulus by agent and dose; and (3) accuracy in data collection with careful consideration to which parameters will be evaluated.

As active antiemetic agents have become available, more questions have arisen. Antiemetic control has been improved, but is not optimal. The necessary studies have yet to be performed comparing the best single agents with the combination regimens that appear most promising. To date, acute chemotherapy-induced emesis is the problem most widely examined. Few studies have addressed the problem of anticipatory emesis [23, 24].

New agents or studies are needed to improve current antiemetic control, to provide more convenient treatment regimens and to identify useful regimens for patients who have not done well with prior antiemetic treatments. Additionally, trials are needed to determine which available antiemetics and at which dosage schedules are best against the emesis produced by specific chemotherapeutic agents.

The more successful antiemetic studies of the past few years have focused on agents, doses, schedules or routes of administration that were

not generally used prior to 1980. Further trials with the more effective agents are likely to result in improved control of emesis.

REFERENCES

1. Carey MP, Burish TG, Brenner DE. Delta-9-tetrahydrocannabinol in cancer chemotherapy: research problems and issues. *Ann Intern Med* 1983, **99**, 106–114.
2. Gralla RJ. Metoclopramide. A review of antiemetic trials. *Drugs* 1983, **25**, 63–73.
3. Wampler G. The pharmacology and clinical effectiveness of phenothiazines and related drugs for managing chemotherapy-induced emesis. *Drugs* 1983, **25**, 35–51.
4. Frytak S, Moertel CG, O'Fallon J *et al.* Delta-9-tetrahydrocannabinol as an antiemetic in patients treated with cancer chemotherapy: a double comparison with prochlorperazine and a placebo. *Ann Intern Med* 1979, **91**, 825–830.
5. Orr LE, McKerman JF, Bloone B. Antiemetic effect of tetrahydrocannabinol. *Arch Intern Med* 1980, **140**, 1431–1433.
6. Chang AE, Shiling DJ, Stillman RC *et al.* Delta-9-tetrahydrocannabinol as an antiemetic in patients receiving high-dose methotrexate: a prospective, randomized evaluation. *Ann Intern Med* 1979, **91**, 819–824.
7. Gralla RJ, Itri LM, Pisko SE *et al.* Antiemetic efficacy of high-dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. *N Engl J Med* 1981, **305**, 905–909.
8. Homesley HD, Gainey JM, Jobson VN *et al.* Double-blind placebo-controlled study of metoclopramide in cisplatin-induced emesis. *N Engl J Med* 1982, **307**, 250–251.
9. Cassileth PA, Lusk EJ, Torri S *et al.* Antiemetic efficacy of dexamethasone therapy in patients receiving cancer chemotherapy. *Arch Intern Med* 1983, **143**, 1347–1349.
10. Sallan SE, Cronin CM, Zelen M *et al.* Antiemetics in patient receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *N Engl J Med* 1980, **302**, 135–138.
11. Gralla RJ, Tyson LB, Bordin LA *et al.* Antiemetic therapy: a review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. *Cancer Treat Rep* 1984, **68**, 163–172.
12. Neidhart J, Gagen M, Wilson H *et al.* Comparative trial of the antiemetic effects of THC and haloperidol. *J Clin Pharmacol* 1981, **21**, 38S–42S.
13. Grunberg SM, Gala KV, Kampenfeld M *et al.* Comparison of the antiemetic effects of high-dose intravenous metoclopramide and high-dose intravenous haldol in a randomized double-blind crossover study. *Proc ASCO* 1983, **2**, 85.
14. Frustaci S, Tumolo S, Tirell U *et al.* High-dose metoclopramide versus dexamethasone in the prevention of cisplatin induced vomiting. *Proc ASCO* 1983, **2**, 87.
15. Aapro MS, Plezia PM, Alberts DS *et al.* Double-blind crossover study of the antiemetic efficacy of high-dose dexamethasone vs high-dose metoclopramide. *Proc ASCO* 1983, **2**, 93.
16. Lewin M, Meyer B, Drayer M *et al.* Optimizing metoclopramide control of *cis*-platinum induced emesis. *Proc ASCO* 1983, **1**, 97.
17. Kris MG, Tyson LB, Gralla RJ *et al.* Extrapyramidal reactions with high-dose metoclopramide. *N Eng J Med* 1983, **309**, 433.
18. Lane R, McGee R, Rivkin S. Antiemetic combination (BCDVR) for control of platinum induced emesis. *Proc ASCO* 1982, **1**, 65.
19. Plezia PM, Alberts DS, Aapro MS *et al.* Immediate termination of intractable cisplatin induced vomiting with an intensive 5-drug antiemetic regimen. *Proc ASCO* 1983, **2**, 93.
20. Kris MG, Gralla RJ, Tyson LB *et al.* Improved control of cisplatin-induced emesis with high-dose metoclopramide and with combinations of metoclopramide, dexamethasone and diphenhydramide: results of consecutive trials in 255 patients. *Cancer* In press.
21. Mason BA, Dambra J, Grossman B *et al.* Effective control of cisplatin-induced nausea using high-dose steroids and droperidol. *Cancer Treat Rep* 1982, **66**, 243–245.
22. Tyson LB, Gralla RJ, Clark RA *et al.* Combination antiemetic trials with metoclopramide. *Proc ASCO* 1983, **2**, 91.
23. Morrow GR. Prevalence and correlates of anticipatory nausea and vomiting in chemotherapy patients. *JNCI* 1982, **68**, 585–588.
24. Morrow GR, Morrell C. Behavioral treatment for the anticipatory nausea and vomiting induced by cancer chemotherapy. *N Engl J Med* 1982, **307**, 1476–1480.