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Potential for Combination Therapy with the New Antiserotonergic Agents

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Appreciation of the major role played by serotonergic (5-HT_3) neuroreceptors in the emetic reflex arc has introduced an additional factor into the rational design of combination antiemetic therapy. Combinations of an antidopaminergic agent and a corticosteroid have previously served as the basis for many successful antiemetic regimens. Three pilot studies and three randomised studies have now demonstrated potentiation of antiemetic activity of a 5-HT_3 antagonist by dexamethasone as well. Further development of combination antiemetic regimens may involve antagonism of additional receptors including those for benzodiazepines, opiates, and catecholamines. Even antidopaminergic agents may continue to have a role. Although high-dose metoclopramide has both antiserotonergic and antidopaminergic activity, other pure antidopaminergic agents retain significant antiemetic activity. The combination of an antiserotonergic agent and a low-dose antidopaminergic agent has already shown promise in one pilot study. Newer and more effective antiemetic combinations will be needed to continue to improve the quality of life of patients receiving chemotherapy.
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INTRODUCTION

THE MECHANISM that controls the emetic response can be likened to a neural reflex arc, unique only in that this reflex arc contains multiple afferent limbs. Three afferent pathways are of particular importance in vomiting induced by chemotherapy [1]. The humoral limb includes chemical substances carried by the bloodstream and the cerebrospinal fluid to the chemoreceptor trigger zone as well as neural pathways from the chemoreceptor trigger zone to the vomiting centre in the brainstem. The peripheral pathway consists of nerve endings in the gastrointestinal wall which carry impulses through vagal pathways to the vomiting centre. Finally the cerebral cortical pathway includes learned phenomena associated with prior emetogenic responses (sights, smells, sounds or memories) that activate neural impulses from the cerebral cortex to the vomiting centre. From the vomiting centre a single set of efferent pathways activates the effector organs of the thorax and abdomen that initiate the emetic act.

Antiemetic control is, therefore, a matter of disrupting the emetic reflex arc. In the setting of multiple afferent pathways, achieving this goal is made more difficult by the necessity to either identify the appropriate afferent limb or limbs for each chemotherapeutic challenge or to effectively block all of the potential afferent limbs simultaneously. A rationale for selection of appropriate pharmacological agents has been provided by the recognition that different anatomical sites contain high concentrations of different types of neural receptors. Historically most attention was directed toward dopaminergic (D2), muscarinic cholinergic and histaminergic receptors [2]. Histaminergic and cholinergic receptors are found in the vomiting centre. Cholinergic and dopaminergic receptors are found in the gastrointestinal wall. Dopaminergic receptors are also found in high concentration in the chemoreceptor trigger zone.

Antiemetic agents can, therefore, be described in terms of the neural receptors affected. Scopolamine has anticholinergic activity. Diphenhydramine and promethazine have antihistaminergic activity. Dopaminergic neurons were long considered to be of particular importance in view of their concentration in both the gastrointestinal tract and the chemoreceptor trigger zone, two of the major sites of initiation of this reflex arc. Thus, many antiemetic agents including phenothiazines, butyrophenones, and substituted benzamides, have significant antidopaminergic activity.

Successful combination antiemetic therapy requires use of various antiemetic agents with complementary rather than redundant activity. Broad-spectrum blockade as well as more effective blockade of individual sites is thereby obtained. After the description of significant antiemetic activity with high-dose metoclopramide [3], further success in improving antiemetic activity was achieved by combining high-dose metoclopramide with corticosteroids such as dexamethasone. In 1984 Allan [4] performed a randomised double-blind study comparing high-dose metoclopramide with or without dexamethasone for the prevention of cisplatin-induced vomiting. The addition of dexamethasone caused significant improvement in numerous parameters including complete control of retching and vomiting, major control of retching and vomiting (<3 episodes), complete control of nausea, major control of nausea and duration of nausea. Grunberg [5] performed a similar randomised double-blind crossover study of metoclopramide with or without dexamethasone for the prevention of cisplatin-induced vomiting and also noted a marked improvement with

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dexamethasone in increasing the number of patients achieving complete protection from vomiting.

As described earlier in this symposium, identification of 5-HT_3 receptors in the gastrointestinal tract and to a lesser extent in the central nervous system and development of various 5-HT_3 blocking agents has altered our approach to antiemesis. High-dose metoclopramide has been recognised as having both antiserotonergic and antidopaminergic activity [6]. It is, therefore, logical that the first attempts to improve the antiemetic efficacy of the 5-HT_3 blocking agents should parallel those with high-dose metoclopramide and involve combinations with corticosteroids. Six studies suggesting improved antiemetic efficacy with a 5-HT_3 blocking agent/corticosteroid combination have now appeared. Carmichael *et al.* [7] performed a dose ranging study of granisetron in which this agent was given at doses of 10, 20, 30 or 40 μg/kg to patients receiving cisplatin. Patients receiving the 10 or 20 μg/kg dose of granisetron also received four doses of dexamethasone 4 mg. The median number of vomiting episodes was 6.5 for the patients receiving granisetron 10 μg/kg plus dexamethasone, 0 for patients receiving granisetron 20 μg/kg plus dexamethasone, 3 for patients receiving granisetron 30 μg/kg alone, and 0 for patients receiving granisetron 40 μg/kg alone. Thus, the addition of dexamethasone appears to shift the response curve of granisetron and improve the relative efficacy of lower doses. Cunningham [8] performed a study that suggested improved efficacy for ondansetron with the addition of dexamethasone. 8 patients (6 receiving cisplatin) who had had unsatisfactory responses to ondansetron alone in terms of nausea or vomiting episodes received ondansetron plus dexamethasone on the subsequent course of chemotherapy. None of the patients vomited after the combination therapy and 7 of the 8 patients demonstrated improvement in nausea or vomiting. Smith [9] also examined the combination of ondansetron plus dexamethasone. 14 patients (10 receiving cisplatin at a dose of 75 mg/m^2) who had had more than five vomiting episodes both with single agent ondansetron and with a combination of dexamethasone plus metoclopramide were treated with ondansetron plus dexamethasone. 9 patients had complete protection from vomiting with the new combination.

These three studies were suggestive of a combined effect of 5-HT_3 blocking agents and corticosteroids. Three additional randomised double-blind crossover studies have now confirmed this effect. Roila [10] performed the first definitive study of the role of dexamethasone in these combinations. 102 patients receiving cisplatin at a dose of at least 50 mg/m^2 (average 76 mg/m^2) were randomised between ondansetron 0.15 mg/kg intravenously every 2 h × 3 with or without dexamethasone 20 mg intravenously. 89 patients completed the crossover. A significant advantage for the combination was seen in complete protection from vomiting (64 vs. 91%, $P=0.0005$), complete protection from nausea (66 vs. 89%, $P<0.0025$), and complete protection from both nausea and vomiting (56 vs. 81%, $P<0.0008$). Of the patients expressing a preference, significantly more preferred the combination therapy (14 vs. 39%, $P<0.003$). Smith [11] performed a similar randomisation in 31 patients with metastatic germ cell tumour (30 male, 1 female; median age 28.5 years) receiving a 4-day course of chemotherapy including vincristine and methotrexate on day 1, bleomycin on days 2 and 3, and cisplatin 120 mg/m^2 on day 4. Ondansetron 8 mg orally every 8 h for 8 days beginning on day 1 was given with or without dexamethasone 8 mg orally every 8 h for 2 days beginning on day 4 (2 h before cisplatin). Observations for acute cisplatin-induced emesis were made on days 4 and 5. Among the 27 patients completing the crossover, complete or major protection (2 or fewer vomiting episodes) was seen more commonly with the combination (30 vs. 78%, $P=0.001$). A lesser grade of nausea was also seen more commonly with the combination ($P<0.001$). Smyth *et al.* [12] treated 100 patients receiving cisplatin 100 mg/m^2 with ondansetron 8 mg intravenously followed by 1 mg/h intravenously continuous infusion for 24 h with or without dexamethasone 20 mg intravenously. 71 patients completed the crossover and were fully evaluable. Once again the combination resulted in more patients with complete or major protection from vomiting (56 vs. 69%, $P=0.035$), a lesser grade of nausea ($P=0.003$), and greater patient preference (21 vs. 54%, $P=0.017$)

The question now arises as to which other agents should be considered for inclusion in combination antiemetic therapy with the 5-HT_3 blocking agents. The anxiolytic lorazepam is commonly used in combination antiemetic regimens with high-dose metoclopramide and adds a dimension of cerebral cortical blockade. This may be particularly important in preventing anticipatory vomiting and in preventing protracted vomiting related to reinforcement by the vomiting act itself. Ondansetron has been suggested to also have independent anxiolytic activity [13]. Combinations of this agent with a benzodiazepine specifically to prevent or treat anticipatory vomiting might, therefore, be considered. Catecholamine blocking agents might also be of interest since Fetting [14] has recently described a correlation between anticipatory vomiting and noradrenergic activity.

The 5-HT_3 blocking agents are presently being considered as possible replacements for high-dose metoclopramide that will provide equivalent antiemetic efficacy without antidopaminergic toxicity. However these agents may not be completely redundant and the possibility of a role for combination therapy with antidopaminergic agents and 5-HT_3 blocking agents should be considered. Costall [15] emphasised the antiserotonergic activity of metoclopramide by demonstrating that both ondansetron and metoclopramide markedly increase gastric emptying in the guinea pig while haloperidol, a specific antidopaminergic agent, does not increase gastric emptying. However, one must remember that butyrophenones such as haloperidol are indeed effective antiemetic agents. Thus, an antiemetic role for antidopaminergic agents independent of crossover antiserotonergic activity can be postulated. Bregni [16] has reported a pilot study of the 5-HT_3 antagonist tropisetron combined with haloperidol in 26 patients treated with high-dose cyclophosphamide or high-dose melphalan. The median number of vomiting episodes in the first 72 h was three (compared to six in a previous series with tropisetron alone). The addition of transdermal scopolamine for some of these patients made no appreciable difference. Further careful studies of 5-HT_3 blocking agents combined with antidopaminergic agents (such as low-dose metoclopramide) would indeed be interesting.

One interaction that would not be desirable would be antagonism by an antiemetic agent against the antineoplastic activity of the chemotherapeutic agent. Aapro *et al.* [17] previously demonstrated that dexamethasone does not alter the activity of cisplatin against P388 leukaemia. Fortunately, a lack of antagonism between a 5-HT_3 blocking agent and a chemotherapeutic agent has now also been suggested. Goddard

et al. [18] examined possible effects of granisetron against the activity of cisplatin. No compromise of cisplatin activity was seen in an ADJ/PC6 plasmacytoma model, an L1210 leukaemia model, or an HX/110 ovarian carcinoma model.

Several different compounds with significant 5-HT_3 blocking activity have now been demonstrated to be effective antiemetics, confirming the importance of the 5-HT_3 receptor as a mediator of the emetic response. Investigation of potential antiemetic combinations that provide complementary and, therefore, broader spectrum coverage of the emetogenic pathways should lead to promising developments in the next several years.

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