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Clinical evaluation of the simultaneous blockade of the dopamine D-2, Histamine H-1, and muscarinic cholinergic receptors in cancer chemotherapy-induced emesis: Results of a controlled trial

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Summary. Twenty-six patients being treated with 5-fluorouracil-adriamycin-cyclophosphamide (FAC), or vincristine-adriamycin-cyclophosphamide (VAC) chemotherapy completed a randomized, double-blind, cross-over study in which the antiemetic activity of thiethylperazine (6.5 mg p.o. every 8 h $\times 5$ days) was compared with that of the combination of thiethylperazine (same dosage) plus amitriptyline (25 mg p.o. every 8 h $\times 5$ days). This combination was designed to obtain a simultaneous blockade of the dopamine D-2, histamine H-1, and muscarinic cholinergic receptors of the central structures responsible for emesis (chemoreceptor trigger zone and vomiting center).

The combination significantly decreased both the number of emetic episodes ($P<0.05$) and the duration of emesis ($P<0.01$) compared with thiethylperazine alone. The combination was also preferred by a significantly higher number of the patients ($P<0.001$) who were exposed to both the types of antiemetic treatment under trial.

The combination of thiethylperazine plus amitriptyline was shown to have a satisfactory antiemetic activity against vomiting induced by VAC chemotherapy in males; it afforded major protection (two emetic episodes or fewer) in 83% of the cases. Nonetheless, it cannot be considered a satisfactory treatment for the control of vomiting induced by FAC chemotherapy in female patients, only 43% of whom achieved major antiemetic protection.

Introduction

Nausea and vomiting are the most frequent and unpleasant side effects of cancer chemotherapy. The need to obtain efficient antiemetic treatment for the emesis induced by antitumor chemotherapy is, therefore, urgent.

The phenothiazine derivatives (conventional antiemetics) have been shown to have a higher activity than placebo against vomiting induced by 5-fluorouracil [8, 9], but are of little or no value in the control of emesis induced by chemotherapeutic combinations [14]. The antiemetic activity of phenothiazines appears to be linked to the blockade of dopamine D-2 receptors in the chemoreceptor trigger zone (CTZ) [5]. The demonstration of a high concentration of H-1 histamine and muscarinic cholinergic receptors in structures closely linked to the vomiting center (nucleus tractus solitarius, dorsal motor nucleus of the vagus, nucleus ambiguus) [11, 16] has suggested to Peroutka and Snyder [13] that these receptors may also be involved in the triggering of the emetic response. According this hypothesis, the usual failure of conventional antiemetic (antidopaminergic) treatments could be related to their inability to block H-1 histamine and muscarinic cholinergic receptors of the central structures of the emesis. For this reason, these authors claimed that the emesis induced by antineoplastic chemotherapy could be more appropriately controlled by means of a phenothiazine (a D-2 dopamine blocker) combined with a tricyclic Antidepressant (an H-1 histamine and muscarinic cholinergic blocker). To assess this hypothesis, we carried out a controlled clinical trial comparing the antiemetic activity of the combination of a phenothiazine plus a tricyclic antidepressant with that of phenothiazine alone in vomiting induced by adriamycin-cyclophosphamide combinations.

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Materials and methods

Twenty-eight patients (14 men suffering from small cell lung cancer and 14 women suffering from breast cancer) entered this randomized, double-blind, cross-over study. All patients included had experienced vomiting (without antiemetic treatment) in the first course of chemotherapy. The characteristics of the patients and the chemotherapy treatment are shown in Table 1. All the patients received treatment as outpatients and gave fully informed consent before the second course of chemotherapy.

After stratification according to the chemotherapy received, in the second course with the same chemotherapy (first of the trial) the patients were randomized to receive one of the two types of antiemetic treatment being compared:

A: Thiethylperazine (one 6.5-mg tablet p.o. every 8 h $\times 5$ days) plus amitriptyline (one 25-mg tablet p.o. every 8 h $\times$ 5 days).

B: Thiethylperazine (same dose as in A) plus placebo, indistingishable from amitriptyline, containing lactose (one tablet p.o. every 8 h $\times$ 5 days).

The first antiemetic dose was received at 8.00 a.m. on the day of chemotherapy. The cytotoxic drugs were administered i.v. starting at 11.00 a.m. for a period of 60–90 min. In order to maintain the double-blind design each antiemetic treatment was identified with a code, in

Table 1. Characteristics of the patients and chemotherapy

Total number of patients	28
Group 1	
Number of patients	14
Males	14
Neoplasm: Small cell lung cancer	
Treatment: VAC:	
Vincristine 1.4 mg/m2 i.v. day 1	every 3 weeks
Adriamycin 50 mg/m2 i.v. day 1	every 3 weeks
Cyclophosphamide 750 mg/m2 i.v. day 1	every 3 weeks
Median age (range 51–67 years)	58
Group 2	
Number of patients	14
Female	14
Neoplasm: Breast cancer	
Treatment: FAC:	
5-Fluorouracil 500 mg/m2 i.v. day 1	every 3 weeks
Adriamycin 50 mg/m2 i.v. day 1	every 3 weeks
Cyclophosphamide 500 mg/m2 i.v. day 1	every 3 weeks
Median age (range 36–65 years)	47

such a way that neither the patients nor the investigators in charge of the control of emesis knew its nature.

In the third course with the same chemotherapy (second of the trial) the patients received the antiemetic treatment he or she had not had before, so that each patient served as his/her own control. The patients were asked to fill in a specially designed questionnaire on the evolution of the emesis, recording each emetic episode and its time of occurrence. The potential side effects of the antiemetic treatment were also recorded. After the third course of chemotherapy (second of the trial) the patients expressed their preference for one of the two antiemetic treatments received in two consecutive courses of chemotherapy.

For the analysis of the results, the signed rank Wilcoxon test was used to compare the number of emetic episodes and the duration of emesis. The differences in the preferences shown by the patients and in the toxicity were analyzed using the Chi-square test.

Results

Of the 28 patients included in the trial, 26 (12 men and 14 women) received both types of antiemetic treatment and were considered evaluable. Two patients receiving VAC chemotherapy gave up the treatment after the first course of the trial and were lost to follow up. The data on emesis in these patients are not available, since they were excluded from the trial.

The results obtained in the trial are shown in Fig. 1. The combination antiemetic treatment had higher antiemetic activity than thiethylperazine alone, resulting in a statistically significant reduction in the number of vomiting episodes and in the duration of emesis. These results were independent of the order in which patients received the antiemetic agents (both antiemetic regimens were given equally frequently as first treatment and no differences in emesis were observed between the first and second courses of study). In addition, a statistically significant percentage of patients (65%versus 12%; $P<0.001$) expressed their preference for the combination antiemetic treatment after receiving both classes of treatment under trial.

Men receiving VAC chemotherapy experienced a greater degree of protection than women receiving FAC chemotherapy. In fact, the major antiemetic protection rate (percentage of patients with 0–2 vomiting episodes) obtained with the combination of antiemetics was 83% for the subgroup treated with VAC and 43% for the female patients treated with FAC. With thiethylperazine the corresponding percentages were 58% (VAC) and 14% (FAC).

The incidence of side effects of the antiemetic treatments was higher with the combination than with thiethylperazine alone. Sedation appeared in 88% of the courses with thiethylperazine-amitriptyline and 27% of the courses with thiethylperazine-placebo ($P<0.0001$). Similarly, the percentage of patients who reported dry mouth was higher with the combination than with thiethylperazine (73% vs 49%), although this difference was not statistically significant ($P=0.087$).

Discussion

The control of vomiting induced by antineoplasic chemotherapy has been the object of several trials, especially since 1977 [12]. Although unquestionable progress has been made in this field in recent years, we are still far from satisfactory solutions for control of the emesis induced by the majority of the antineoplasic drugs. Generally, the conventional antiemetic drugs (phenothiazines) are considered of little value in the control of emesis induced by chemotherapy combinations, so much so that only 21% of

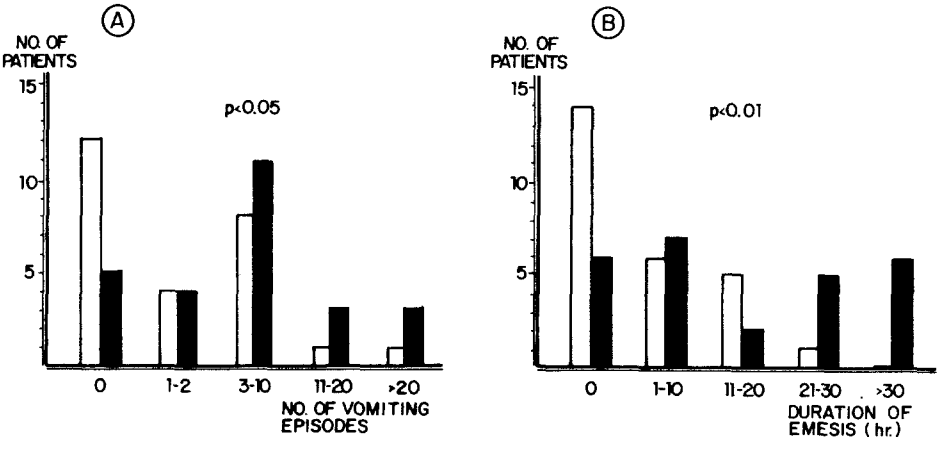

Fig. 1 A, B. Number of vomiting episodes **(A)** and duration of emesis **(B)** during treatment with thiethylperazine (■) or antiemetic combination (□). Patients with 0 or 1 vomiting episodes were considered as having a duration of emesis of 0 h

investigators consider that they are always beneficial for this purpose [12].

At present, high-dose i.v. metoclopramide [4, 15], corticoids [3, 6], and antiemetic combinations appear to be the most promising spheres of research in the control of emesis induced by antineoplasic chemotherapy.

The combination of antiemetics constitutes an attractive and little explored sphere of clinical research, although their rationale has still not been satisfactorily established.

In 1979, Morran et al. [10] proved the antiemetic superiority of the combination of a phenothiazine (fluphenazine) and a tricyclic antidepressant (nortriptyline) over fluphenazine alone in the control of CMF-induced vomiting in patients suffering from breast cancer. These authors attributed this potentiating effect of nortriptyline, which had not previously been described, to the relief of the frequent psychological symptoms from which these patients suffer. However, Peroutka and Snyder [13] later offered a very different explanation for this phenomenon, suggesting that the superiority of the combination could be due to the simultaneous blockade of the D-2 dopamine, H-1 histamine and muscarinic cholinergic receptors located in the central structures responsible for emesis.

In order to give further support to this hypothesis, we designed the present controlled trial, in which the antiemetic efficacy of the combination of a phenothiazine plus a tricyclic antidepressant different from the ones used by Morran et al. [10] (thiethylperazine plus amitriptyline) was compared with that of thiethylperazine alone in vomiting induced by combinations of adriamycin-cyclophosphamide, which are frequently used in clinical medicine. The results obtained bear out the antiemetic superiority of the combination of thiethylperazine and amitriptyline over thiethylperazine alone in vomiting induced by chemotherapy combinations and gives further support to Peroutka and Snyder's hypothesis of the implication of receptors other than the D-2 dopaminergic in the emetic response. Even though the number of patients included in the trial was small, some partial conclusions of interest can be drawn. Although the combination was superior to thiethylperazine alone, its antiemetic potency can only be classified as moderate. The combination of thiethylperazine and amitriptyline appears to be a sufficiently protective antimetic treatment against vomiting induced by moderately emetogenic polychemotherapy treatments, such as the VAC combination in male patients. In this group an adequate control of the emesis was achieved (0-2 vomiting episodes) in 83% of cases. In contrast, and spite of its superiority over thiethylperazine, the combination was not shown to be a sufficiently protective treatment against vomiting induced by the FAC combination in female patients, since only 43% of these patients experienced major protection.

A possible explanation for the moderate antiemetic activity of the combination of thiethylperazine plus amitriptyline is that neurotransmitters other than those above mentioned could be involved in the emetic response. For example, the endogenous opiate receptors present in high concentrations in the CTZ and in the fasciculus solitarius [1, 2] and probably involved in the emesis were not affected by the pharmacological activity of the combination of thiethylperazine and amitriptyline.

Recently, Mellink et al. [7] reported the results of a controlled trial comparing the activity of a similar combination of antiemetics (fluphenazine plus amitriptyline) with that of metoclopramide in vomiting induced by Adriamycin combinations. The group of patients studied was made up mainly of female patients suffering from breast cancer, who were being treated with Adriamycin-cyclophosphamide or FAC, and male patients suffering from small cell lung cancer, who were being treated with cyclophosphamide-adriamycin-etoposide. Although the combination was slightly superior to metoclopramide, the difference was not statistically significant. The combined treatment was preferred to metoclopramide by a higher number of patients who completed the two phases of the trial, this difference being statistically significant only at $P<0.1$. The authors concluded that the combination of flufenazine and amitriptyline did not seem to be an efficient antiemetic treatment. Nevertheless, and although the antiemetic treatment was only maintained for 24 h, 94% of the men (most of whom were receiving treatment with cyclophosphamide-Adriamycin-etoposide) had fewer than six vomiting episodes with the antiemetic combination (against 76% with metoclopramide), while the women (being treated with FAC or Adriamycin-cyclophosphamide) experienced significantly less antiemetic protection with both types of antiemetic treatments. Therefore, it seems that a subgroup of patients (males suffering from small cell lung cancer) could have achieved acceptable control of emesis with the combination of antiemetics, as in our trial.

Morran et al. [10] proved the antiemetic superiority of the combination of fluphenazine plus nortriptyline vs over fluphenazine, metoclopramide, cyclicine or placebo in CMF chemotherapy-induced emesis. In spite of the low doses of antiemetics given (fluphenazine 1.5 mg a day and nortriptyline 30 mg a day), 53% of the patients treated with the combination of antiemetics had no vomiting, while 75% of those treated with the other antiemetics or placebo in the trial did.

The combination of a phenothiazine plus a tricyclic antidepressant is not, therefore, a panacea in the control of cancer chemotherapy-induced emesis, since its antiemetic potency appears to be inadequate against the most highly emetogenic chemotherapeutic combinations; but its simplicity and lack of dangerous side effects make it interesting in the treatment of vomiting induced by moderately emetogenic chemotherapy. New trials are necessary to define the exact indications for this type of antiemetic combination.

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