Eur J Cancer Clin Oncol, Vol. 20, No. 9, pp. 1147–1150, 1984.
Printed in Great Britain.

0277-5379/84$03.00+0.00

Amitriptyline plus Fluphenazine to Prevent Chemotherapy-induced Emesis in Cancer Patients: a Double-blind Randomized Cross-over Study

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Abstract—*In a population of 51 ambulant cancer patients treated with doxorubicin-containing chemotherapy we conducted a double-blind cross-over randomized trial, comparing the anti-emetic efficacy of a combination of amitriptyline (25 mg p.o. q 6 hr × 4) and fluphenazine (2.5 mg p.o. q 6 hr × 4) (AF) with that of metoclopramide (20 mg q 6 hr × 4) (M). Thirty-three out of the 51 patients vomited less than six times during treatment with AF as opposed to 26/51 with M. This difference was not significant. However, 55% of patients preferred AF to M, compared to 30% with the reverse preference (P < 0.1). The main side-effect was drowsiness, which patients reported significantly more frequently when on AF. With both anti-emetic regimens men vomited less frequently than women. The combination of amitriptyline and fluphenazine, though theoretically attractive, did not appear to be an effective anti-emetic regimen in the dose and schedule given.*

INTRODUCTION

CANCER patients treated with chemotherapy often experience nausea and vomiting as a most distressing side-effect which can detrimentally interfere with their quality of life. Recently high-dose metoclopramide has been shown to effectively reduce CDDP-induced nausea and vomiting [1, 2]. However, this regimen requires hospitalization and some authors report toxicity in up to 20% of treated patients [3, 4]; moreover, its usefulness in reducing emesis not induced by CDDP has been questioned [5]. Therefore there is still a need to investigate other anti-emetic treatments which can be administered to outpatients and are less toxic.

The precise emetogenic site of action of the various chemotherapeutics is not known [6]. Peroutka and Snyder [7] suggested, however, that nausea and vomiting may be reduced by a combination of drugs with a high affinity for the dopaminergic, cholinergic and histaminergic receptors in the Chemoreceptor Trigger Zone which play a role in the emetogenic process [8]. Morran *et al.* [9] tested this hypothesis by using a combination of fluphenazine and nortriptyline which has a high affinity for the receptors mentioned above [7, 10]. They reported this combination to effectively reduce both incidence and severity of nausea and vomiting.

The aim of our study was to further test the 'receptor-blocking hypothesis' in outpatients treated with doxorubicin containing polychemotherapy. We therefore conducted a randomized double-blind cross-over trial comparing the anti-emetic efficacy of fluphenazine and amitriptyline, a combination with high affinity for dopaminergic, histaminergic anc cholinergic receptors, with that of oral metoclopramide.

MATERIALS AND METHODS

Patient population

Fifty-one patients were admitted to the protocol (34 female, 17 male), all over 30 yr of age and all of them receiving doxorubicin containing chemotherapy for a variety of malignancies (see Table 1). Of 46 patients the first two courses of treatment were studied, whereas the remaining five patients had already received one or more courses of chemotherapy before entering the study. Patients with glaucoma, intracranial disease and those already on treatment with antipsychotic or

Accepted 2 March 1984.

Table 1. Patient characteristics

Type of malignancy	No. of patients	Chemotherapy
Breast cancer, stages II, III	17	cyclophosphamide (500 mg/m²) doxorubicin (40 mg/m²) 5-FU (500 mg/m²)
Breast cancer, stage IV	11	cyclophosphamide (500 mg/m²) doxorubicin (50 mg/m²)
Small cell lung cancer	13	cyclophosphamide (1000 mg/m²) doxorubicin (50 mg/m²) etoposide (100 mg/m²)
Non-Hodgkin's lymphoma	4	cyclophosphamide (750 mg/m²) doxorubicin (50 mg/m²) vincristine (1.4 mg/m²) prednisone (100 mg × 5)
Pancreatic carcinoma	2	(4'-epi)doxorubicin
Miscellaneous	4	various doxorubicin containing combinations

antidepressant drugs were not admitted; patients receiving CDDP-containing chemotherapy were also excluded.

Anti-emetic regimen

After explaining the purposes of this study and obtaining verbal consent, patients were randomly and blindly assigned to either the amitriptyline–fluphenazine combination (AF) or metoclopramide (M). For their next course they were crossed over to the other treatment. The AF combination contained 25 mg amitriptyline and 2.5 mg fluphenazine, while M was given in dosages of 20 mg. Both anti-emetics were administered orally in white capsules at the following times: 1 hr before and 5, 12 and 21 hr after the start of chemotherapy.

Evaluation

Each patient was telephoned by the protocol staff the day following chemotherapy and asked about the duration and severity (mild/moderate/severe) of their nausea and to what extent this interfered with their normal daily life activities. The number of vomiting episodes were recorded and the total duration of the period of emetic symptoms, as well as side-effects experienced by the patient (including drowsiness, blurred vision, dry mouth, extrapyramidal symptoms, etc.). Other parameters measured for toxicity purposes were CBC, liver function tests and blood pressure. After both regimens had been given, patients were asked to choose their regimen of preference.

RESULTS

Numbers of vomiting episodes during treatment with AF or M are given in Fig. 1. Although

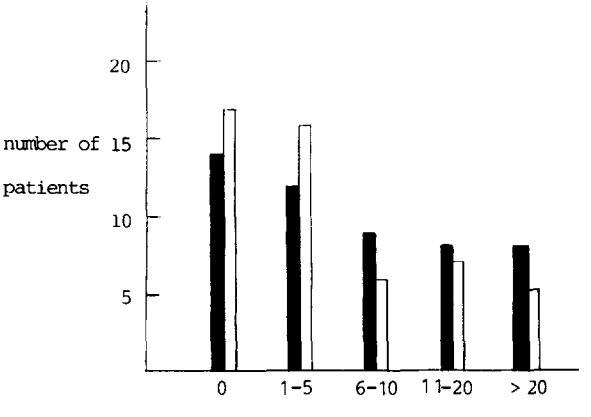

Fig. 1. Number of vomiting episodes during treatment with metoclopramide (■) or AF (□).

AF appears to be slightly superior to M in suppressing emesis, this difference was not significant ($\chi^2 = 1.4, P > 0.1$); this was true for the population as a whole as well as for any subset of patients analyzed. Within the limits of our evaluation techniques, duration and severity of nausea were not significantly different between the two treatment arms and generally severity was reported to be moderate. Both regimens were given equally frequently as first treatment and no differences in severity of nausea and vomiting between the first and second cycles were observed. Nineteen (37%) patients had a better anti-emetic response (i.e. number of vomiting episodes at least five times less than with the alternative treatment) on AF and 12 (24%) on M, and for 20 (39%) patients no difference in response between the two regimens was recorded. However, 55% of patients preferred AF to M, compared to 30% with the

Table 2. Frequency of vomiting episodes in male and female patients

Antiemetic treatment	No. of patients with less than 6 vomiting episodes	
	Males	Females
Metoclopramide	13 (76)	15 (44)
Amitriptyline–fluphenazine	16 (94)	16 (47)

Nos in parentheses refer to percentages.
Differences between males and females are statistically significant at the $P = 0.06$ (metoclopramide) and $P < 0.001$ (amitriptyline–fluphenazine) levels.

reverse preference; this difference is statistically significant at the $P < 0.1$ level.

The main side-effect was drowsiness, which patients reported significantly more frequently while treated with AF (24/51) than while treated with M (12/51) ($P = 0.02$). There was no relation between the choice of preference and the occurrence of drowsiness. The majority of patients had a dry mouth during both treatments. Two patients reported a short period of blurred vision when treated with AF. No effect of AF or M was observed on blood cell counts, liver function or blood pressure.

Interestingly, with both anti-emetic regimens men experienced significantly less nausea and vomiting than women, although all were treated with a similar combination chemotherapy containing doxorubicin and cyclophosphamide as the most emetogenic agents in a similar schedule and dosage (Table 2).

DISCUSSION

In contrast to what has been suggested in the literature, we did not find a combination of amitriptyline and fluphenazine to be an effective regimen to prevent chemotherapy-induced nausea and vomiting [7, 11]. Close to 35% of the patients still vomited at least six times in 24 hr after chemotherapy, and the combination did not appear to be superior to low-dose oral metoclopramide, which is considered to be of only limited anti-emetic value in these patients [12]. On the other hand, the majority of patients did prefer AF to M, apparently on subjective grounds; a similar dissociation between reported numbers of vomiting episodes and patient experience has been reported for other agents such as cannabinoids [13, 14]. Morran *et al.* [9] reported a difference of around 30% in the frequency of non-vomiting patients between metoclopramide and nortriptyline–fluphenazine. With the latter combination more than 50% of patients were rendered free of vomiting. However, their investigations only refer to female patients receiving cyclophosphamide, methotrexate and 5-fluoruracil (CMF), a combination which may be less emetogenic than doxorubicin-containing chemotherapy. Moreover, its emetogenic properties may at least in part be mediated by psychological pathways, as is suggested by its frequent association with the occurrence of anticipatory vomiting [15, 16]. It may therefore well be that the usefulness of combinations of tricyclic antidepressants and neuroleptics in the doses and schedules employed is limited to patients receiving chemotherapy lacking potent emetogenic cytostatics such as CDDP, doxorubicin and DTIC.

So far, few risk factors predicting for the occurrence and severity of therapy-induced emesis have been identified; to these belong the type of drugs given and psychological factors. In this study we identified a hitherto not described risk factor, namely being female. In our study most male and female patients differ in diagnosis and type of chemotherapy. As far as the chemotherapy is concerned, these differences are probably of only little importance. For the majority of females chemotherapy included 5-fluorouracil as compared to VP-16 for the males; both agents, in the doses employed, are relatively nonemetogenic. Moreover, most males received the two most emetogenic drugs, doxorubicin and cyclophosphamide, in even higher doses. Given the well-known psychological components of chemotherapy-induced nausea and vomiting, the differences in diagnosis may well be of importance, probably in conjunction to other differences as to how male and female patients deal with both the presence of malignant disease and the administration of chemotherapy. Finally, endocrine-determined differences in the reactivity to emetogenic stimuli cannot be ruled out. Further investigations are needed to confirm this finding and assess its importance for the development of effective anti-emetic treatments.

Combination anti-emetic therapy based on affinity for the major receptors in the chemoreceptor trigger zone remains an attractive route for further investigations [17]. Our failure to identify major anti-emetic activity of a dopaminergic, histaminergic and cholinergic blocking combination may, at least in part, be due to inadequate dosages and/or scheduling. The relative paucity of side-effects does appear to allow an intensification of administration or the addition of other drugs with different mechanisms of action in order to find a regimen which is relatively non-toxic and enables administration to outpatients.

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