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A Pilot Study of High-dose Domperidone as an Antiemetic in Patients Treated with Cisplatin

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Abstract—*A dose-finding multicenter study was undertaken to evaluate the antiemetic efficacy of domperidone, an antidopaminergic drug, which has been proposed as a suitable alternative to high-dose metoclopramide in the control of cisplatin-induced nausea and vomiting. Forty-five patients were treated with different increasing high doses of domperidone* (30, 60, 120 *or* 150 mg) *administered by i.v. infusion over* 20 min *every* 2 hr *for a total of four doses for each patient, starting* 30 min *before chemotherapy. The number of episodes of emesis, the duration of nausea and vomiting and side-effects were recorded. Results do not suggest any specific difference in protective effect between the regimens tested. Moreover, occurrence of serious side-effects indicated that the safety of high-dose domperidone is doubtful.*

INTRODUCTION

IN THE search for more active and safer drugs to be used for the control of the emetic effects of chemotherapeutic treatments, especially those including cisplatin, domperidone has been proposed as a suitable alternative to the highly effective high-dose metoclopramide. The claimed advantages of domperidone would be on the safety side: its supposedly low capacity of crossing the blood-brain barrier (shown in animal models) should be expected to produce [1, 2] less central nervous system-related side-effects. Reports on high-dose regimens of domperidone have been dubious with respect to efficacy, however, with no clear indication on the range of effective doses, and somehow worrying in terms of incidence and severity of side-effects [3-5, 7]. A dose-finding multicenter study was therefore undertaken to contribute to the clarification of the above issues.

MATERIALS AND METHODS

Forty-five consecutive patients from the five centers participating in the study, with histologically confirmed cancer were entered into the study. Patients were eligible independently of previous chemotherapeutic treatment if they had a P.S. > 60% on the Karnofsky scale and if they were being treated with a regimen containing high-dose cisplatin ($\geqslant$50 mg/m^2). In the case of a combination regimen the other drugs were administered 24 hr after the cisplatin infusion. Patients with organic disease of the gastrointestinal tract, cardiac disease, psychosis, cerebral metastasis, nausea and vomiting from other causes, or under treatment with radiotherapy, narcotics or other SNC depressants were excluded.

Pretreatment evaluation included physical examination, a complete blood count, a biochemical profile and an electrocardiogram, and this evaluation was repeated 24 hr after each treatment. Cisplatin was generally administered in a 15 to 20-min infusion after previous hydration and after 12.5 g of mannitol i.v.

Patients eligible for the study received domperidone, administered by i.v. infusion over 20 min, at doses of 30 (15 patients), 60 (15 patients), 90 (14 patients), 120 (9 patients) or

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150 mg (1 patient) every 2 hr for a total of four doses for each patient, starting 30 min before chemotherapy. In each of the five centers participating in the study, treatment was started with the lowest dose of domperidone for the first three patients and then continued with the next highest dose for the next three patients, and so on. Of the patients nine received more than one treatment; the total number of treatments was thus 54.

Side-effects of the antiemetic therapy were recorded as referred by the patients and in a specific questionnaire. Such an evaluation was made every 2 hr for the first 8 hr and again at 24 hr after chemotherapy. For each patient the number of episodes of emesis and the duration of nausea and vomiting were recorded every 2 hr for 8 hr and again at 24 hr after chemotherapy.

Statistical analysis

Various linear models have been fitted to the data by means of the statistical package GLIM [6]. The number of vomiting episodes, the duration of nausea and the duration of vomiting have been successively considered as dependent variables. Suitable transformations have been performed on the data, where necessary, and appropriate error structures have been assumed. The degree of good fit of the models has been assessed by means of the analysis of deviance.

RESULTS

Characteristics of the 45 patients entered into the study are shown in Table 1. The primary sites of cancer were: 24 ovary, five lung, four head and neck, three cervix, two body of the uterus, two esophagus and one case each of bladder, testis and penis. There was one patient with osteosarcoma and one with malignant melanoma.

Table 1. Characteristics of patients

No, of patients	45
Age (yr)	
14-40	4
41-50	11
51-60	17
61-70	11
71-72	2
Sex	
Male	12
Female	33
Previous antiblastic therapy	
Yes, without vomiting	24
Yes, with vomiting	4
No	17
Cisplatin dose (mg/m²)	
30-50	2
51-80	26
81-100	16
>100	1

Table 2. Side-effects

Side-effects	Reported by the patient	Reported in the questionnaire
Sedation	8	21
Dry mouth	3	21
Headache	1	5
Vertigo	2	3
Diarrhea	8	12
Abdominal cramps	3	11
Abdominal distension	3	3
Restlessness	2	8
Palpitation	0	5
Tremors	0	5
Perspiration	2	2
Hot flush	2	2
Lacrimation	1	1
Asthenia	1	1
Blurred vision	1	1
Hiccups	2	2
Shivers	2	2
Trismus	1	1
Cardiorespiratory arrest	2	0
Total	44	106

Side-effects are documented in Table 2. The antiemetic activity of domperidone, expressed as number of vomiting episodes occurring at different doses and as length of vomiting and of nausea, is reported in Figs 1-3. These results do not suggest any specific protective effect at any one of the regimens tested. The highest dosage schedule was applied to only one patient, a 60-yr-old woman being treated with cisplatin for a stage III ovarian carcinoma. She experienced cardiorespiratory arrest with cyanosis and was

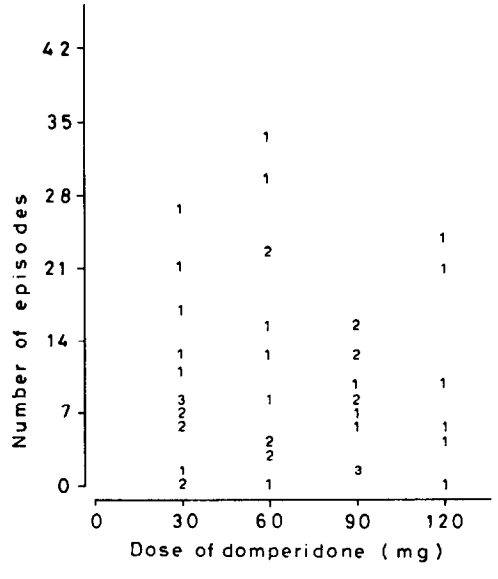

Fig. 1. No. of vomiting episodes by dose of domperidone.

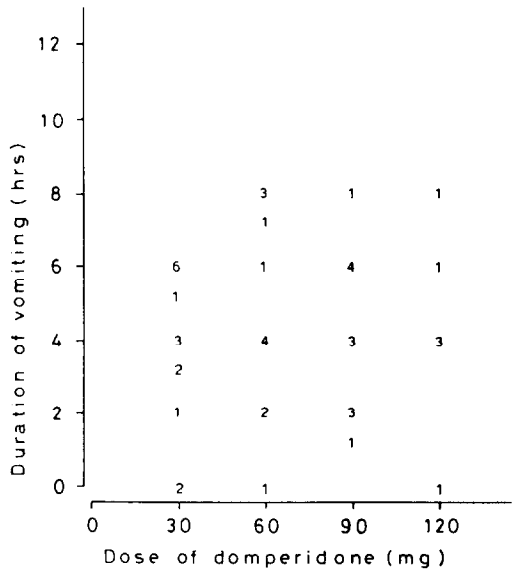

Fig. 2. Duration of vomiting (hr) *by dose of domperidone.*

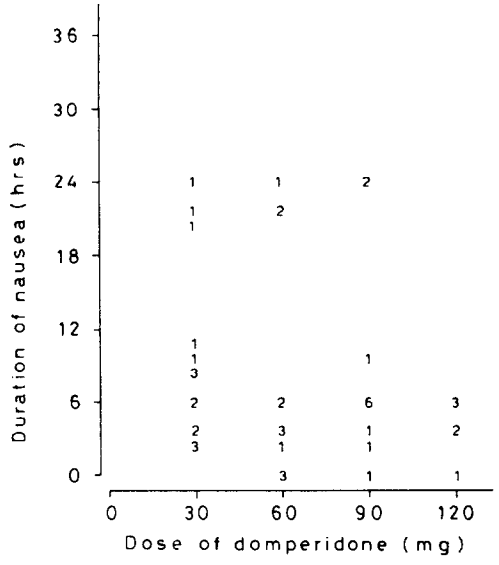

Fig. 3. Duration of nausea (hr) *by dose of domperidone.*

unconscious 10 min after the first infusion of 150 mg of domperidone. Cardiopulmonary respiration was immediately initiated and the cardiorespiratory activity resumed in 1–2 min, accompanied by a transient blood pressure elevation and an extrasystolic arrythmia at auscultation. An ECG performed a few minutes later showed only S-T segment anomalies. Recovery was uneventful. The event prompted, however, the interruption of the study, both because of the lack of efficacy which was becoming apparent through the increasing doses, and because two other serious adverse events had been registered in the meantime in two other patients. A 68-yr-old woman with ovarian cancer suffered a respiratory arrest 90 min after the third infusion of 120 mg of domperidone. The episode lasted for about 1 min and was accompanied by cyanosis and loss of consciousness. Spontaneous, complete recovery was followed by a transient blood pressure rise and persistent amnesia of the episode. An ECG did not show any consistent abnormality. An extrapyramidal reaction in the form of a trismus occurred in a 40-yr-old patient with ovarian carcinoma after the third aministration of 120 mg of domperidone. Five milligrams of diazepam were administered i.v. and the trismus lasted only a few minutes. It was decided not to administer the fourth dose. The other side-effects shown in Table 2 could not be correlated to the different doses of domperidone because of the small number of patients.

As expected, side-effects were reported more frequently in the questionnaire than in direct questioning by the physician. Data analysis using the GLIM confirm the absence of any positive effect of domperidone. Throughout the analysis, domperidone, sex and previous antiblastic therapy have been taken as factor variables on four (the four doses), two (males and females) and two (yes, no) levels, respectively. Let us first consider the number of vomiting episodes. The simple model with the general mean only determines a deviance of 314.1 with 44 degrees of freedom. The inclusion of domperidone in the model (after having allowed for the mean) determines a deviance of 298.8 with 41 degrees of freedom (the first level of domperidone has been taken as the reference category). Hence the test statistic has an approximate chi-squared distribution with 3 degrees of freedom and has value (197.5–193.0)/3 = 1.5. Significance is not achieved ($P > 0.05$). If cisplatin, sex, previous antiblastic therapy and age are considered as possible confounding variables and we include domperidone in the model after having allowed for their effects, the test statistic takes the value of 2.06 on three degrees of freedom, and is again not significant at the 5% level. Residual plots for both models did not show any abnormal feature.

The same type of analysis was performed on the duration of vomiting and of nausea. In these cases, too, significance was not achieved at the 5% level, either for domperidone alone (the values of the statistics being 0.31 and 2.80 for duration of vomiting and of nausea, respectively) or when allowance was made for the confounding variables (the values of the test statistics being 0.63 and 3.88 for duration of vomiting and of nausea, respectively).

The coefficients of previous antiblastic therapy were tested when allowance was made for domperidone. The values of the t statistics were -0.222, -1.683 and -0.6927 for the number of

vomiting episodes, duration of vomiting and duration of nausea, respectively. Since their absolute value does not exceed the critical value of $t(40,0.975) = 2.02$, we do not reject the hypothesis of the coefficients being zero.

DISCUSSION

The formal testing of various increasing dosage schedules of domperidone confirms the scanty, if any, activity of domperidone against cisplatin-induced vomiting and nausea. On the other hand, the use of high-dose domperidone and the schedule of its administration determined the occurrence of serious side-effects. Among these, of particular relevance are the two episodes of cardiopulmonary arrests. The occurrence of such serious side-effects prompted us to interrupt the trial. Important, too, is the finding of an extrapyramidal reaction which imposes important doubts about the safety of domperidone with respect to central nervous system-related adverse reactions. Our experience, together with recent reports regarding a possible cardiotoxicity of high-dose domperidone [8, 11], seem to make further investigations of the use of such doses of domperidone in cisplatin-treated patients not warranted.

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