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Cytostatic-Associated Vomiting Effectively Inhibited by Domperidone (R 33 812)

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Summary. *The effect of domperidone on vomiting due to cytostatic treatment was studied during a double-blind trial involving 41 patients. One group received the sequence domperidone-placebo and the other the reverse sequence during two consecutive courses of cytostatic therapy (chlormethine alone or in combination with other cytostatics). Domperidone 2 mg/ml or the placebo was injected IV 1 h before the start of the cytostatic treatment. A similar injection was given 4 h later. Presence, duration, and incidence of nausea and vomiting before, during, and after the peak period (period from the second up to and including the sixth hour after cytostatic injection) were measured. With respect to vomiting, domperidone was significantly superior to placebo concerning duration and effect before and after the peak period in both sequences. There was no difference during the peak period.*

With respect to nausea, domperidone was superior to placebo concerning duration and effect during the peak period in the placebo-domperidone sequence. No difference was observed in the reverse order. A significant superiority of domperidone was noted before the peak period.

Introduction

Emesis is the most common side-effect associated with the use of cytostatic chemotherapy. This problem can be so troublesome in some patients that it interferes with the feasibility of an adequate treatment programme. Some help is available for the prevention of cytostatics-associated vomiting, but, in general, the treating physician's aim is primarily to limit the impact of the problem on his patient and on his therapy, rather than to completely abolish the nausea and vomiting. Various drugs are available for this purpose. However, it is clear that both antihistamines and antiemetic neuroleptics have their own limitations due to side effects and also to lack of effect in some patients. Therefore, we were tempted to evaluate the possible usefulness of a new antiemetic agent, domperidone (R 33 812, Fig. 1) for the treatment of emesis due to the use of chlormethine in combination with other cytostatic drugs.

In animal pharmacology experiments (Janssen Pharmaceutica, personal communications), domperidone showed potent antiemetic properties, similar in strength and mechanism of action (i.e., blocking of dopamine receptors) to neuroleptic drugs with known antiemetic effects, such as haloperidol [1, 4] and metoclopramide [6]. In contrast to these neuroleptic drugs, however, a striking dissociation was found between the antiemetic effects of domperidone and its effects on the central nervous system. This dissociation appeared to be due to a very poor penetration of the new drug through the blood-brain barrier. Further animal studies (Janssen Pharmaceutica, personal communications) showed that domperidone has a very wide safety margin in both acute and chronic toxicity experiments. It could, therefore, be hoped that this novel substance would be as effective as the available antiemetic drugs, and that it would not give rise to annoying side effects even in relatively high doses. Evidence already exists that the drug is effective and very well tolerated in adults complaining of chronic dyspepsia associated with delayed gastric

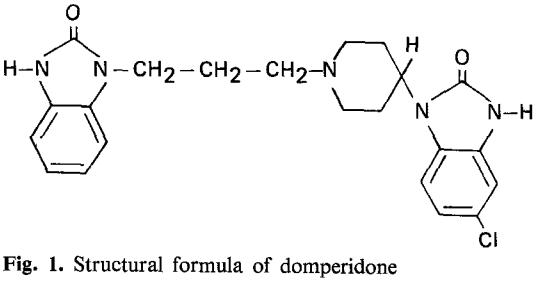

Fig. 1. Structural formula of domperidone

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emptying and in some patients, presenting with vomiting ([3, 5]; Van de Mierop et al., unpublished data).

The primary aim of this study, therefore, was to evaluate the possible antiemetic effects of relatively high doses of domperidone in patients vomiting due to intensive cytostatic chemotherapy. At the same time, the side-effect liability of these high doses was evaluated and an attempt was made at a qualitative estimate of domperidone's antiemetic effects on this condition.

Materials and Methods

Patients

Forty-one patients receiving cyclic IV treatment with 10 mg chlormethine, combined in all but one case (a patient with bronchial carcinoma) with 2 mg vincristine (the MOPP regimen), were selected for this study. The diagnosis in these patients was Hodgkin's or non-Hodgkin's lymphoma, except for the one patient being treated for bronchial carcinoma.

All patients had vomited during previous identical treatments and were to receive at least two more treatment courses. Further patient data are given in Table 1.

Treatment and Design

During the study, the cytostatic chemotherapy remained unchanged for each patient.

The patients were randomly divided into two groups. One group received the sequence domperidone-placebo and the other received the reverse sequence during two consecutive courses of cytostatic therapy. This treatment was strictly double-blind and the medication was separately packed for each patient. The dosage was as follows: 8 ml parenteral solution, containing either 16 mg domperidone (2 mg/ml) or the placebo, was injected IV 1 h before the start of the cytostatic treatment, and a similar injection was given 4 h later.

Other drugs with known or potential antiemetic effects were prohibited until 2 h after the last administration of the double-blind trial.

Assessments

From the first administration of the double-blind medication on, the presence of nausea and vomiting was recorded every hour until 12 h after the start of the cytostatic treatment. The following data were used for the statistical evaluation of the results:

1. Duration of nausea and vomiting, i.e., the time during which these side effects occurred.

2. In order to evaluate the possible differential effect of domperidone treatment on very severe and on less severe nausea and vomiting:

a) The number of times these phenomena were registered from the second hour up to and including the sixth hour after the cytostatics were given, i.e., the peak period of severe nausea and vomiting (about three-quarters of the patients showed at least one of these phenomena during this period).

b) The incidence of nausea and vomiting before and after the peak period, i.e., (i) from the start of the cytostatic chemotherapy to hour 2; and (ii) from hour 7 to hour 12.

As cytostatic chemotherapy itself may be associated with so many side effects, no special check-list for the possible domperidone-related adverse effects was used. However, adverse effects other or more severe than those found in previous similar treatments in the same patients were to be considered as possibly domperidone-induced, and were consequently carefully recorded.

Statistics

Possible maldistributions due to the randomization procedure were evaluated by means of the Mann-Whitney *U*-test and two-tailed probability, regarding age and body weight.

Possible influences of the drug sequences (domperidone → placebo, or the reverse) on the effects observed were evaluated by means of the Kolmogorov-Smirnov two-tailed two-sample test. The Wilcoxon matched-pairs signed-ranks test was used to evaluate the results.

Results

When the double-blind code was broken it was seen that the two treatment sequences had been given to patient groups who were comparable in diagnosis, age and, body weight ($P > 0.05$).

1. Global Effect on the Duration of Nausea and Vomiting (Table 2)

The statistical evaluation of the data related to the presence of nausea was hampered by a drug sequence effect,

Table 1. Patient data

	Number of patients (total no. = 41)
Sex: male	32
female	9
	Median value (range)
Age (years)	55 (43–68)
Weight (kg)	68 (46–95)

Table 2. Results of treatment: duration of symptoms

Treatment group according drug sequence		Duration of symptom (median + range)	
		Nausea	Vomiting
Domperidone–placebo	D[a]	2 (0–9) h	2 (0–8) h
	P	0 (0–8) h	3 (0–8) h
Placebo–domperidone	D	0 (0–5) h	0 (0–6) h
	P	3 (0–7) h	3 (0–7) h
All data[b]	D	NR	1 (0–8) h
	P	NR	3 (0–8) h

[a] D: Domperidone treatment; P: Placebo treatment

[b] NR: Not relevant (because of influence of drug sequence)

Table 3. Results of treatment: incidence of target symptoms

Treatment group according to drug sequence		Incidence of symptom (no. of patients and no. of episodes)											
		Before peak				During peak				After peak			
		Nausea		Vomiting		Nausea		Vomiting		Nausea		Vomiting	
		Patients	Episodes	Patients	Episodes	Patients	Episodes	Patients	Episodes	Patients	Episodes	Patients	Episodes
Domperidone–placebo	D[a]	0	0	1	1	15	35	15	44	4	8	1	2
	P	2	2	3	3	8	23	11	32	3	5	6	8
Placebo–domperidone	D	2	2	0	0	6	17	7	17	1	1	2	2
	P	5	5	4	4	16	45	16	42	5	9	4	8
All data[b]	D	2	2	1	1	NR	NR	22	61	5	9	3	4
	P	7	7	7	7	NR	NR	27	74	8	14	10	16

[a] D: domperidone treatment; P: placebo treatment
[b] NR: Not relevant (because of influence of drug sequence)

as there was no difference between the active drug and the placebo in the domperidone-placebo sequence. However, domperidone was clearly superior ($P < 0.01$) to the placebo when given in the reverse sequence.

However, the drug sequence did not appear to interfere with the data related to the duration of vomiting. Domperidone was superior to the placebo in reducing vomiting ($P < 0.02$).

2. *Possible Differential Effect*

a) Effect during the Peak Period (Table 3). The treatment sequence affected the results concerning nausea in a similar way to the way it affected its duration: the placebo did not differ from domperidone if domperidine was given first, but it was clearly inferior ($P < 0.01$) to the active drug if when the order was reversed.

As the treatment sequence did not appear to influence the data concerning vomiting, the total population was used for the analysis. However, no significant difference was found ($P > 0.10$) between the placebo and domperidone.

b) Effect before and after the Peak Period (Table 3). The drug sequence did not interfere with these results for either parameter and for either observation period.

1. During the pre-peak period, domperidone was found to be significantly superior to the placebo ($P < 0.03$) in preventing both nausea and vomiting.

2. After the peak period, there was some trend toward superiority of domperidone regarding nausea, though the difference was not significant ($P < 0.09$). However, significant superiority of the active drug was demonstrated during this observation period in prevention of vomiting ($P < 0.02$).

3. *Side Effects*

No untoward effects occurred that could be conclusively assigned to the treatment given in the double-blind trial.

Discussion

Interpretation of the data is hampered to some extent by the finding that the drug sequence appeared to influence some results concerning the presence of nausea. It is probably not coincidence that this problem occurred with nausea, which is more easily influenced by psychological factors than vomiting. The presence of such psychological factors is further suggested by the fact that some patients did not report nausea even though they were vomiting and, also by the finding of relatively less nausea if the placebo was preceded by active (i.e., domperidone) treatment during the previous course of cytostatic chemotherapy. In spite of this, the data seem to suggest at least some effect of domperidone on nausea before and after the peak period.

The analysis of the data concerning the more objective symptom of vomiting produced clear evidence that domperidone treatment may considerably shorten the duration of this side effect of intensive chemotherapy. Moreover, as could be expected with this severe type of emesis, the drug did not seem to affect vomiting during the peak period, but was found to be substantially effective in reducing this symptom before and after that time.

Though it appears that domperidone is clearly valuable in the protection of patients against the emetic effects of potent cytostatic drugs, its effectiveness seems limited to the less severe periods of emesis associated

with such drugs. These findings may suggest that better protection can be achieved if less potent cytostatics are used. In addition, when the more potent ones are used, the subjective results of domperidone prophylaxis may be quite noticeable, as the patient experiences a significantly shorter period of sickness. Furthermore, the antiemetic effects of domperidone on this condition may seem only marginally superior to those of drugs like haloperidol and metoclopramide, but if one keeps in mind the very limited side effect liability of the new drug as shown by our own and earlier data ([3, 5]; Van de Mierop, unpublished data), the advantages of domperidone over the available agents are quite obvious.

The dose of 16 mg domperidone seemed to be well chosen for a normal range of body weights, as neither the therapeutic result nor the occurrence of adverse effects seemed to depend upon the weight of the patients (data not shown).

It is not entirely clear how domperidone can counteract the emetic effects of cytostatic drugs. It may be relevant, however, to recall that irradiation has been shown to inhibit gastric emptying in rat [2], and it is quite conceivable that cytostatic drugs, certainly the alkylating ones like chlormethine, have a similar effect. It is of interest, therefore, that domperidone appears to enhance gastric emptying, especially if it is delayed (Janssen Pharmaceutica, personal communications) and that the clinical usefulness already reported with this drug was found in a condition associated with symptoms of decreased gastric emptying ([3, 5]; Van de Mierop, unpublished observations).

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