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Double-blind randomized cross-over trial comparing methylprednisolone with placebo in chemotherapy-induced nausea and vomiting: a study with special reference to efficacy parameters

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Sixty-one patients with breast cancer who received chemotherapy participated in a double-blind randomized cross-over study with methylprednisolone (MP) 250 mg as a single i.v. injection before chemotherapy and placebo as antiemetic treatment. The determining efficacy parameter was preference. Other parameters used were a visual analogue scale for nausea, a categorical four-point nausea intensity scale recorded by a nurse observer, emetic amounts, emetic episodes, acceptance of nausea and vomiting, and global assessments for nausea and vomiting. MP showed a significant antiemetic effect compared with placebo which was most pronounced for moderately emetogenic chemotherapy. The visual analogue scale, emetic amounts, acceptance and global assessments were easy to handle and showed coherence with preference, whereas nausea intensity and emetic episodes were resource demanding to record and showed no coherence with preference. It is concluded that for a precise evaluation of nausea and vomiting the visual analogue scale and emetic amounts are most reliable; for ambulatory patients global assessments seem to be sufficient.

Key words: Antiemetics, evaluation, nausea, vomiting, cancer chemotherapy, methylprednisolone, placebo.

Introduction

During the last 10 years numerous trials have been published concerning the treatment of nausea and vomiting secondary to cancer chemotherapy, and certain progress has been made with regard to treatment results, especially following the use of high dose metoclopramide in cisplatin-induced nausea and vomiting,[1] and the introduction of the 5-HT_3 antagonists.[2]

Steroids were introduced as antiemetics in 1979 by Baker *et al.*,[3] but until now few trials comparing the effect of steroids with placebo have been published.[3–6] Three of these trials have shown superiority of steroids over placebo; however, the studies are not very detailed in their evaluation of efficacy and the study populations are rather small. Steroids as a single drug have not shown any effect in patients treated with cisplatin.[7–9]

No consensus exists concerning the most suitable parameters for the evaluation of antiemetic effects. Minimally, nausea and vomiting should be evaluated separately as they may be two different behaviors.[10]

It is important to find methods of evaluation which are reliable, valid, simple, easy to handle and which can be repeated for prolonged time intervals. It is our impression from the present and previous studies that many patients prefer to be ambulatory instead of hospitalized, and may feel their nausea and vomiting aggravated by frequent evaluation. Therefore, it was obvious to us to investigate the value of both an elaborate and a more simple evaluation of antiemetic efficacy in conjunction with a comparative study of methylprednisolone (Solu-Medrol[R]) (MP) and placebo.

Therefore, the aims of the present study were (1) to test the antiemetic efficacy of MP 250 mg i.v. before chemotherapy compared with placebo in a double-blind randomized cross-over set-up, (2) to register various parameters for antiemetic efficacy and examine their connection, and (3) to study different methods of evaluation in order to find the most simple and valid ones.

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Materials and method

Design

The investigation was designed as a randomized double-blind cross-over study comparing MP 250 mg with placebo given 30 min before chemotherapy as a 15 min infusion. The period of evaluation was 24 h. All patients were hospitalized on the day of chemotherapy, which they received around 10 a.m., and they left the hospital the next morning.

Patients

Included in the study were 61 patients receiving adjuvant chemotherapy with cyclophosfamide, methotrexate and 5-fluorouracil (CMF) every 4 weeks, or relapse therapy either with the CEF regimen (same as CMF but with methotrexate replaced by epirubicin) or with epirubicin (E) as single-drug therapy every 3 weeks. Doses are given in Table 1.

Inclusion criteria

All patients had experienced nausea and vomiting with prior chemotherapy and had received antiemetic treatment with chlorpromazine and/or metoclopramide 10–20 mg given orally, i.v. or rectally on demand, and if indicated lorazepam 1–2 mg orally.

The patients were considered capable of participation in two study courses.

Exclusion criteria

Patients receiving continuous steroid therapy for any reason, patients with severe hypertension, diabetes, tuberculosis, CNS tumors, reasons for nausea and vomiting other than chemotherapy, or a history of psychiatric illness were not included.

Patients who did not go through two study courses or whose dosages of chemotherapy were changed by more than $\pm 25\%$ between course 1 and 2 were excluded from analysis.

Drop out patients

Patients who received unidentical doses of benzodiazepines in the two study courses or who received chlorpromazine in both courses were considered as drop outs, and were analyzed separately because of the difficulty in the interpretation of patients' preference.

Table 1. Patient material

	Number of patients	
Included	61	
Non-eligible: steroid treatment (1), diabetes (1), inability to cooperate (2)	4	
Eligible	57	
Age, years median (range): 58 (33–70)		
Excluded after course 1 because of reduced dose of chemotherapy (1), own wish (4), pituitary tumour (1), treatment stopped due to progressive disease (1)	7	(6 CEF, 1 CMF)
Drop outs after course 2 because of chlorpromazine in both study arms	6	(all CEF)
Drop outs after course 2 because of unidentical doses of benzodiazepine in the two study arms	8	(5 CEF, 1 CMF, 2 E)
Drop out after course 2 because of a technical error (wrong sequence of placebo–MP)	1	(CEF)
Drop outs and excluded patients, total	22	(18 CEF, 2 CMF, 2 E)
Evaluable	35	(22 CEF, 10 CMF, 3 E)

CMF: cyclophosphamide 600 mg/m^2, methotrexate 60 mg/m^2, 5-fluorouracil 600 mg/m^2.
CEF: cyclophosphamide 600 mg/m^2, epirubicin 40 mg/m^2, 5-fluorouracil 600 mg/m^2.
E: epirubicin 40–90 mg/m^2.

Other medications

Usual medicine was allowed; patients treated with benzodiazepines should receive the same type and dosage during the two study courses. Supplementary antiemetics were not given unless the patients asked for antiemetics; primarily, chlorpromazine suppositories 100 mg were used.

Parameters and evaluation

The following variables for efficacy were obtained. The time schedule is shown in Figure 1.

(1) Patients' preference for the study course with MP or the one with placebo.
(2) Patients' assessment of nausea on a visual analogue scale (VAS), a 100 mm long horizontal line, end-barred, but otherwise unmarked, the ends of which were marked 'No nausea' and 'Unbearable nausea', respectively (Figure 2). Patients were not allowed to see their previous recordings when marking the VAS.
(3) A trained nurse observer's recording of the current nausea intensity (NI) registered on a categorical scale from 0 to 3 (no, slight, moderate, or severe nausea).
(4) A categorical global assessment scale (GA), indicating nausea intensity for the first 8 h and for all 24 h marked by the patient from 0 to 3 (no, slight, moderate or severe nausea).

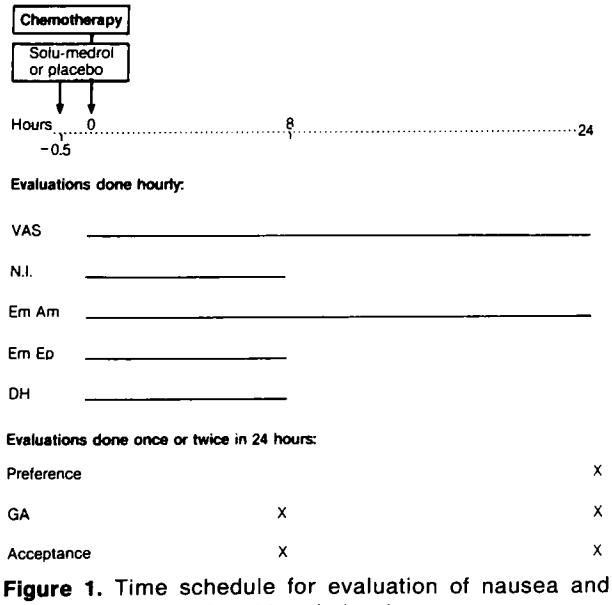

Figure 1. Time schedule for evaluation of nausea and vomiting (see text for abbreviations).

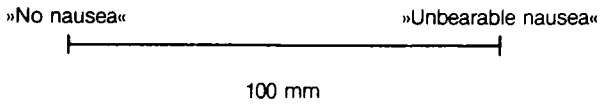

Figure 2. Visual analogue scale (VAS).

(5) Acceptance of nausea (AN): the patients were asked whether they considered the nausea acceptable or not.
(6) Emetic amounts (Em Am) per hour measured in grams.
(7) The number of emetic episodes (Em Ep) per hour.
(8) The number of dry heaves (DH) (feeling like vomiting without bringing up gastric contents) per hour.
(9) A categorical global assessment scale (GA) for vomiting, similar to that for nausea, and recorded at the same hours.
(10) Acceptance of vomiting (AV): the patients were asked whether they considered the vomiting acceptable or not.
(11) Blood pressure and heart rate were measured 3 times, urine analysis for glucose was done in the evening.

A nurse observer was present during the day until 5 p.m., thereafter the evaluations were done by the nursing staff in the department, until the next morning where the final evaluation was done by the nurse observer.

VAS scores and Em Am were obtained hourly for 24 h when the patients were awake. NI, Em Ep and DH were recorded hourly in the daytime while the nurse observer was present. GA's and acceptance were obtained at 5 p.m. for the previous 7–8 h. Preference was obtained the next morning at 9 a.m.

Statistical analysis

Patients' preferences were chosen as the determining parameter and the other parameters were related to preference. If the patients received chlorpromazine in one course, they were assumed to prefer the opposite one. The study was planned with interim analysis of the primary efficacy variable (preference) for every 12 patients (Prescott's test).

For the VAS scores, Em Am and Em Ep, the following methods were used: analysis of carry-over effect, effect of periodicity and effect of treatment, were performed by analysis of variance with 'treatment sequence' and 'type of chemother-

apy' as factors. Effect of treatment was additionally tested by the non-parametric Wilcoxon signed rank test without the assumption of normally distributed data, but assuming that no effect of periodicity exists. For all other tests, either the Fishers' two-sided exact test in r × c unordered tables or Kruskal–Wallis two-sided exact test in ordered r × c table was applied. A significance level of 5% was applied.

Ethics

The patients gave informed consent in accordance with the Helsinki Declaration II. The study was approved by the local ethical committee.

Results

Sixty-one female patients were included in the study. Four patients were non-eligible, seven patients were excluded after course 1 as they did not participate in two study courses. The remaining 50 patients went through two study courses; 15 were drop out patients, due to chlorpromazine in both study arms (six patients), unidentical doses of benzodiazepines in the two study arms (eight patients) and a technical error (wrong sequence of placebo–MP, one patient). Thus, 35 patients were left for analysis, and 15 drop out patients could be analyzed separately.

Among the 35 evaluable patients, 10 received the CMF regimen, 22 received CEF and three received epirubicin. Among the 15 drop out patients, one received CMF, 12 received CEF and one epirubicin (Table 1).

Among the 35 evaluable patients, 18 received placebo–MP and 17 the reverse order. The three patients who received epirubicin were all treated with the sequence MP–placebo and they were excluded from analyses considered to be influenced by the type of chemotherapy.

Seventeen patients received neither benzodiazepine nor chlorpromazine, nine patients received identical doses of benzodiazepine in both courses and 12 patients received chlorpromazine in one course (nine CEF, one CMF and two epirubicin patients) (Table 2).

Preference

Among the 35 evaluable patients, 29 preferred MP and six preferred placebo ($p < 0.001$). MP was preferred by 16 of 22 patients treated with CEF ($p < 0.05$), 10 of 10 patients treated with CMF ($p < 0.01$) and three of three patients treated with epirubicin.

Among the 15 drop outs who went through both study courses, six preferred MP, six placebo and three had no preference. For the whole group (35 completers and 15 drop outs), MP was found to be superior to placebo ($p < 0.001$).

Among the 35 evaluable patients, 12 received chlorpromazine, 10 in the placebo and two in the MP period (Table 2). The patients were defined as preferring the treatment in which chlorpromazine was not given, and in fact this was the case in 10 out of the 12 patients (nine on placebo, one on MP).

Table 2. The administration of chlorpromazine distributed on chemotherapy and treatment sequence in 35 completers

Chemotherapy	Treatment sequence[a]	Number of patients	Chlorpromazine[b]	
			only in course 1	only in course 2
CEF	P MP	14	6	0
	MP P	8	1	2
CMF	P MP	4	0	0
	MP P	6	0	1
E	P MP	0	0	0
	MP P	3	1	1

[a] P = placebo; MP = methylprednisolone.
[b] Chlorpromazine given in 10 patients on placebo, two on MP ($p < 0.01$, two-sided exact test).

Medication in non-completers (drop outs and excluded patients)

Drop outs and excluded patients did not vary from completing patients with regard to age, weight, height, blood pressure or heart rate. They received significantly more chlorpromazine than completers during the MP treatment ($p < 0.05$) (Table 3). This reflects the fact that the non-completers (including the drop outs) represented the patients most bothered by nausea and vomiting, and seemed to be more 'resistant' to MP than completers. No significant difference was seen between completers and non-completers when they received placebo.

Visual analogue scores

No evidence of carry-over effect or effect of periodicity was found.

Table 3. Benzodiazepine and chlorpromazine administration in completing and non-completing patients

	Completers (35)		Non-completers (22)	
	placebo (total 35 periods)	MP (total 35 periods)	placebo (total 20 periods)	MP (total 17 periods)
Chlorpromazine given	10 periods (29%)	2 periods[a] (6%)	10 periods (50%)	6 periods[a] (35%)
Benzodiazepine given	9 periods (26%)	7 periods (20%)	10 periods (50%)	7 periods (41%)

[a] $p < 0.05$, two-sided exact test.

Effect of antiemetic treatment on the VAS scores was tested by analysis of variance on the difference between average VAS scores in each period (period 2 minus period 1).

For the 32 patients (three epirubicin patients omitted) $p < 0.01$ in favour of MP.

In the CEF patients the average VAS score per hour decreased from 14.4 mm during the placebo treatment to 10.7 mm during the treatment with MP, a reduction of around 25%, although eight patients received chlorpromazine during the placebo treatment and only one during the MP treatment.

In the CMF patients, the average VAS score per hour decreased from 8.2 to 3.3 mm with MP, a reduction of around 60%, although one patient received chlorpromazine during the placebo course.

For all 32 patients, the average VAS score decreased from 12.5 to 8.4 mm with MP, a reduction of around 33%.

The course of VAS scores for all patients on placebo and MP is shown in Figure 3. MP decreases the peak of VAS scores 5–15 h after chemotherapy when the results from the two chemotherapy groups are pooled.

The NI scores obtained from 9 a.m. to 5 p.m. only showed 12 scores above 0, six during MP and six during placebo treatment. The NI score the next morning disclosed no effect in favor of MP; 10 patients on MP were recorded to have a NI score above 0 (five scores of 1 and five scores of 2). Six patients on placebo were recorded above 0 (three scores of 1 and three scores of 2). The NI scores as used in the present study were worthless in the evaluation of antiemetic effect.

Emetic amount

No carry-over effect or effect of periodicity was found. Effect of antiemetic treatment on emetic amount was tested in the same way as for VAS scores.

MP had a significant effect on emetic amounts ($p < 0.05$). The average hourly emetic amount in CEF patients was reduced from 36.1 to 23.3 g, around 35%, and in the CMF group from 26.9 to 12 g, around 55%. Figure 4 shows the course of emesis in all 32 patients. Again, MP can be seen to exert its effect particularly on the 'peak of emesis' 5–15 h after chemotherapy.

Emetic episodes

No evidence of any carry-over effect or effect of periodicity was seen. Emetic episodes were registered during the first 6–8 h after chemotherapy,

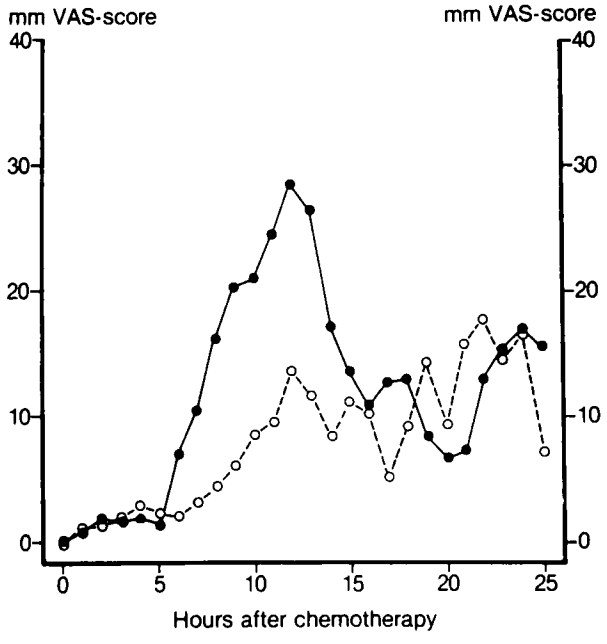

Figure 3. The time course of nausea evaluated by VAS: 32 CEF and CMF patients. (●) Placebo; (○) MP.

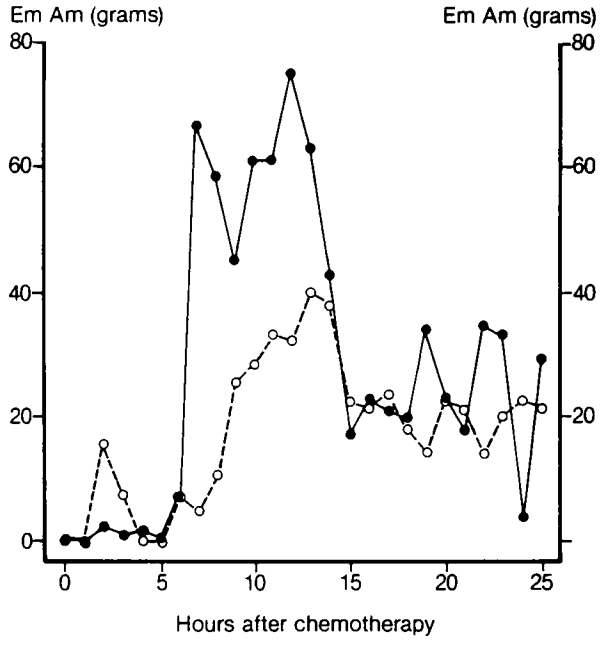

Figure 4. The time course of vomiting evaluated by the emetic amounts: 32 CEF and CMF patients. (●) Placebo; (○) MP.

but in 40 of 70 treatment courses no episodes were observed. No significant treatment effect from MP was detected.

Dry heaves

Dry heaves were recorded in 12 courses and no effect from MP was seen.

GAs and acceptance

No effect of any carry-over or periodicity was found. GA for nausea and vomiting at 5 p.m. and the next morning all showed lower scores after treatment with MP than with placebo. Eight hours after chemotherapy p values for nausea and vomiting were both less than 0.05. For the next morning p values were both less than 0.001 (two-sided exact test).

Acceptance of nausea. No useful interpretation of nausea seemed to be obtained by this question; at least no significant difference between MP and placebo was seen.

Acceptance of vomiting. No significant difference was seen at 5 p.m., but the value the next morning showed a significant difference in favor of MP ($p < 0.05$, two-sided exact test).

The value of VAS and Em Am as efficacy parameters for the 8 h period where Em Ep and NI were recorded

As VAS and Em Am were recorded for 24 h and NI and Em Ep only for 8 h, we analyzed whether VAS and Em Am also were superior to NI and Em Ep in reflecting antiemetic effect for the limited 8 h period. The mean values were reduced from the placebo period to the MP period as follows: VAS from 4.90 to 2.3 mm ($p < 0.05$), NI from 0.0262 to 0.0107 (NS), Em Am/h from 16.5 to 5.4 g ($p < 0.05$) and Em Ep/h from 0.265 to 0.129 (NS). So only VAS and Em Am changed significantly from placebo to MP. When the possible effect of chemotherapy was considered and a Wilcoxon rank sum test aligned for chemotherapy group medians[11] was applied the VAS score revealed a significant treatment effect ($p < 0.05$), whereas Em Am, Em Ep and NI scores did not reveal any significant treatment effect.

Considering only the first 8 h after chemotherapy, the p values for treatment effect on the GAs of nausea and vomiting both were less than 0.05.

Coherence between parameters (Table 4)

VAS scores. The sign of the difference between VAS scores per hour in period 1 and period 2 was calculated and compared with the patients' expressed preference. For 26 of 35 patients, the sign of the VAS score change was in agreement with the patients' preference ($p < 0.01$, by two-sided exact test).

Emetic amount. The sign of the difference between emetic amount per hour between period 1 and period 2 was likewise compared with preference. For 27 of 35 patients, the sign of change in emetic amount was in agreement with the patients' preference ($p < 0.001$ by two-sided exact test). Emetic episodes showed no significant correlation with preference.

Global assessments. The sign of the difference between GAs for nausea 8 h after chemotherapy in period 1 and 2 revealed no agreement with preference, but the sign of the difference between GAs for vomiting 8 h after chemotherapy in period 1 and 2 and for both nausea and vomiting the next morning showed a highly significant agreement with preference ($p < 0.01$, $p < 0.01$ and $p < 0.001$, respectively).

Table 4. Coherence between preference and other parameters: the difference between scores during placebo and methylprednisolone compared with preference (35 patients)

Parameter[a]	Sign of difference in scores in agreement with preference (no. of patients)	No difference in scores (no. of patients)	Sign of difference in scores in disagreement with preference (no. of patients)	Two-sided exact test in ordered tables (p values)
G.N. 5	15	14	6	>0.05
G.N. 9	20	11	4	<0.01
G.V. 5	13	21	1	<0.01
G.V. 9	20	14	1	<0.001
A.N. 9	10	23	2	<0.05
A.V. 9	18	16	1	<0.001
VAS	26	0	9	<0.01
Em Am	27	3	5	<0.001
Em Ep	11	15	9	>0.05

[a] G.N. 5 and 9: global assessment for nausea at 5 p.m. and 9 a.m., respectively; G.V. 5 and 9: global assessment for vomiting at 5 p.m. and 9 a.m., respectively; A.N. 9: acceptance for nausea at 9 a.m.; A.V. 9: acceptance for vomiting at 9 a.m.; VAS: visual analogue scale for nausea, average per hour; Em Am: emetic amount, average per hour; Em Ep: emetic episodes, average per hour.

Acceptance. The sign of the difference between acceptance in period 1 and 2 revealed significant agreement with patients' preference ($p < 0.05$ for nausea and $p < 0.001$ for vomiting) by two-sided exact test.

The number of patients totally free from nausea and vomiting as well as acceptance of nausea and vomiting is shown in Table 5. It is seen that total absence of nausea and vomiting is not a prerequisite for acceptance.

Side effects

Twenty-nine patients did not experience any side effects during treatment with placebo or MP. One patient complained of headache and one of a special taste during both treatments. Four patients experienced side effects during MP treatment: headaches (2), heartburn (1), a taste of spirits (1), and one did not specify her side effects.

Table 5. The number of patients free from nausea and vomiting, and the number who found nausea and vomiting acceptable

	Only during MP	During both treatment periods	*Only* during placebo
Free from nausea and vomiting for 24 h	5	0	0
Nausea and vomiting acceptable for 24 h	15	9	3

Thirty-three patients had a urine analysis performed in both study periods. Sixteen patients had higher urine glucose value during MP, and one patient during placebo treatment.

Discussion

The present study has documented the antiemetic effect from a single i.v. injection of 50 mg MP given 30 min before chemotherapy reflected in preference, VAS, emetic amounts, acceptance and global assessments. The effect was most pronounced with the moderately emetogenic chemotherapy CMF and less impressive with the more emetogenic CEF regimen. The duration of the effect seems to be approximately 15 h.

Antiemetic treatment has become more efficacious over the past 10 years and today we have regimens that are able to keep around 50% of the patients treated even with cisplatin free from nausea and vomiting. Therefore, it is to be expected that future comparative antiemetic studies will have to deal with smaller differences in efficacy. Thus, the situation has changed since Gralla *et al.*[1] published a randomized study with high dose metoclopramide, placebo and phenotiazines. In that study the differences in efficacy were so pronounced that the number of emetic episodes was a sufficient parameter. When we go for smaller differences we have to look for more sensitive methods of evaluation if future studies are to be done with a reasonable number of patients. Therefore, we found it of interest to investigate the value of different

efficacy parameters that could be used in hospitalized or ambulatory patients.

In addition to preference, we have investigated VAS and emetic volume hourly for 24 h, and nausea intensity, emetic episodes and dry heaves hourly during the day time. We also have applied more simple methods—the global assessment for nausea and vomiting, and the question whether nausea and vomiting was acceptable or not. As no objectively true answer exists to the question of how bothered the patient is, we have chosen to let the preference be the determining parameter. Preference is only suitable for comparative studies, and therefore we investigated whether different parameters for intensity of nausea and vomiting were really reflected in the preference. Indeed, both VAS scores and emetic amounts were closely coherent with the preference, whereas the widely used parameters for antiemetic effects, the number of emetic episodes and NI,[12] were without coherence with preference and we were unable to show any difference between MP and placebo.

During the initial phase of the study we tried to count the number of emetic episodes for the whole 24 h period, but it soon appeared to be very difficult to handle. The nursing staff asked the patients once an hour about the number of emetic episodes, but several patients had difficulty in remembering the number. In the daytime the nurse observer was present, but 7–8 h of intense observation after chemotherapy did not give any reliable coherence with preference. On the contrary, the use of a global assessment for vomiting at 5 p.m. (the time when counting of emetic episodes was stopped) seemed to give reasonable information about vomiting. It was easier and more accurate to measure emetic amounts than to count the number of emetic episodes, when both parameters were measured in the same 7–8 h period. It must be admitted that emetic amount depends on ingestion of fluid and solid meals, but in practice it did not seem to influence the results.

In order to explore simpler methods of evaluation, we have investigated the use of a global assessment score for nausea and one for vomiting. We found that they could reflect antiemetic efficacy from MP and agreed with preference.

The present study has a somewhat complicated structure and as a consequence some flaws concerning conduct, analysis and the conclusions that can be derived from it. This stems from the fact that more than one question was addressed in the study.

The primary question—the randomized one—was whether one i.v. injection of MP 250 mg was superior to placebo in controlling nausea and vomiting from non-cisplatin containing chemotherapy, using a double-blind, randomized, repeat series design. The primary efficacy parameter chosen was patients' preference.

Holding this as the basic axis of the study, and because of the repeat series design, the secondary question concerned the importance of a number of methods for evaluation of nausea and vomiting all systematically registered during an 8–24 h observation period. The results of these methods were all rigorously analyzed with regard to their correlation with the determining parameter.

A number of minor points, e.g. use of sedatives, identical doses of chemotherapy in the two treatment series, fall off of patients, etc., have to be considered in this context.

The main result of the study is quite clear. However, as far as the secondary question concerning evaluation methods is concerned a number of further studies specifically aimed at and designed for the evaluation of particular methods will be needed before firm conclusions can be reached.

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