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High Doses of Metoclopramide or Droperidol in the Prevention of Cisplatin-Induced Emesis

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Abstract—*The antiemetic effects of the benzamide metoclopramide (MCL, Paspertin®) and of the butyrophenone droperidol (DRO, Dehydrobenzperidol®) were compared by two sequential analytical trials in cisplatin treated patients. In the first trial (cisplatin 60–90 mg/m²) the drugs were given as loading infusions (MCL 0.5 mg/kg, and DRO 0.05 mg/kg, each per b.w./h over 2 hr), beginning 2 hr before cisplatin administration; this was followed by the maintenance infusion at half the dose, over 24 hr (total dose of MCL 7 mg/kg, and DRO 0.7 mg/kg b.w. per cycle, resp.). During the second trial (cisplatin 90–120 mg/m²) the antiemetic dosages were doubled (total dose of 14 or 1.4 mg/kg per cycle. After 12 and 14 treatment pairs, resp., MCL was significantly ($P < 0.05$) more effective than DRO. Clinically antiemetic protection (i.e. < three vomiting episodes) were seen in 9 of 12 and 13 of 14 patients, resp., compared with only 5 of 12 and 5 of 14 patients on DRO. The incidence of major extrapyramidal side-effects was more than 2-fold higher at DRO. The benefit/risk relationships (i.e. the relation between the prevented emetic episodes and the number of extrapyramidal reactions seen) of MCL were 2.7–3.0-fold better than those of DRO. The relatively higher antiemetic efficacy of MCL may be due to its additional gastrointestinal mechanisms.*

INTRODUCTION

NAUSEA and vomiting during cisplatin occur in almost all patients [1] and may severely limit its use, as patients may be unwilling to complete the chemotherapeutic courses [2]. The antiemetic effectiveness of high-dose metoclopramide (MCL) has been repeatedly demonstrated [3]. The butyrophenone derivative droperidol (DRO), mostly used in neuroleptanalgesia, has been used as an alternate antiemetic treatment against cisplatin emesis [4–7]. The results of these studies at very different dosages and schedules are difficult to interpret. In addition, only little information is available on the high-dose effects of DRO.

Both DRO and MCL are classified as dopamine receptor antagonists with central mechanism of action [8, 9]. MCL, in addition, has a peripheral mode of action on the motilty of the gastrointestinal tract [10]. Both drugs can cause exrapyramidal effects, i.e. EPS [11, 12]. Therefore, we studied the antiemetic efficacy and the side effects of MCL and DRO at different high dosages against different doses of cisplatin. Because of the large doses and expected frequency of adverse reactions the sample size was to be as small as possible. Sequential analysis of matched pairs is an ideal design for such short-term studies [13, 14].

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MATERIALS AND METHODS

Forty-two male patients participated in the study. All gave informed consent. The patients had solid tumors of the testis ($n = 13$, cisplatin 120 mg/m²), of the lung ($n = 19$, cisplatin 90 mg/m²), or of head and neck ($n = 13$, cisplatin 60 mg/m²). All had creatinine clearances above 60 ml/min, none had brain or liver metastases. Patients with anticipatory emesis were excluded.

Cisplatin (study 1 60–90 mg/m²; study 2 90–120 mg/m²) was given together with adriamycin, bleomycin, or vindesine. The only potentially emetogenic cytostatic drug besides cisplatin was adriamycin 50 mg/m². The numbers of treatments per group were 5/12, 5/12, 6/14, and 7/14, i.e. equally attributed.

Patients were admitted the day before chemotherapy and were observed at least 36 hr after termination for signs of complications. Usual medications (digitalis, antihypertensive drugs, bronchodilators, and oral hypoglycemic agents) were

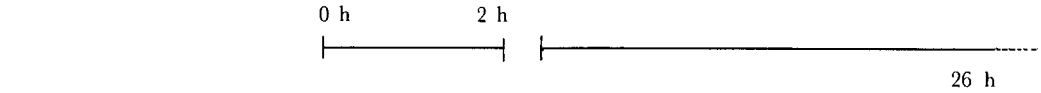
not discontinued. The following drugs were not admitted: sedatives, hypnotics, opiates, antidepressive agents, neuroleptic drugs. All patients received loperamide 2 mg q. 6 hr as antidiarrhoeal therapy.

Figure 1 shows the time course of antiemetic and cytostatic drug administration. All patients were hydrated with 1000 ml/hr for 2 hr, starting at 9.00 a.m. followed by fluids at a rate of 250 ml/hr for 24 hr. Furosemide was used when clinical signs of fluid overload occured. Patients were fasting for the first 12 hr. After the first 2 hr of hydration cisplatin was administered over 30–60 min in 500 ml of normal saline. Other chemotherapeutic drugs were administered according to the used protocol. Severe extrapyramidal symptoms were treated with intravenous biperiden. In the first study (MCL I) metoclopramide was given in a loading infusion of 0.5 mg/kg b.w. per hr over 2 hr, and subsequently as a maintenance infusion of 0.25 mg/kg b.w. per hour over 24 hr. The doses for droperidol (DRO II) were 0.05 and 0.025 mg/kg, resp.. The second trial (MCL II and DRO II) was performed with the doubled doses of MCL I and DRO I. Patients were entered in the study sequentially: two consecutive patients were treated as a pair and were randomized to one of the two drugs previously assigned to set pair, i.e. MCL I vs. DRO I, and MCL II vs. DRO II. The frequency of emesis was counted for each of the two members of a pair by an observer unaware of which treatment regimen was given. The outcome of the matched pairs were plotted on the sequential plan (15) (as depicted in Fig. 2). The treatment causing fewer episodes of vomiting was considered superior. The study was stopped and the code was broken when one of the limiting outer lines were crossed. The threshold probability level was $\alpha = 0.05$.

A standardized questionaire was used to record the frequency and time course of emetic events, duration of nausea, and adverse reactions. The questionaire was completed by observations of the medical staff. In addition the patients subjectively estimated nausea and vomiting on a 4-level verbal scale 'none–mild–moderate–strong'. All assessments were performed 24 hr after treatment was completed by the same investigator who did not know which drugs or dosages were being evaluated. Two historical surveys of patients with the same cancer malignancies and cytostatic treatments, but without satisfactorily antiemetic prophylaxis, were used as reference groups for estimation of the antiemetic efficacy. The first group of patients (cisplatin 60–90 mg/m^2) showed an average frequency of vomiting of 10.0 episodes per treatment cycle with a range of 7–15 (unpublished results), the second group (cisplatin 90–120 mg/m^2) had mean 17.1 (range 7–28) episodes per cycle (unpublished results).

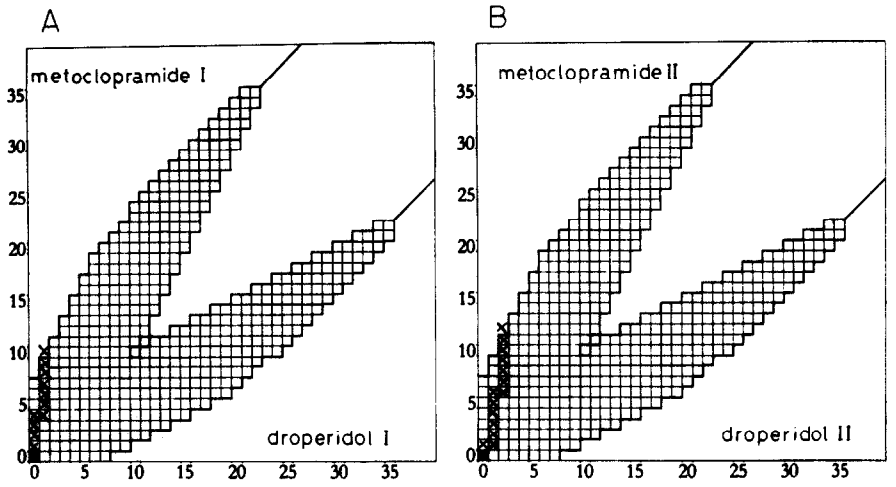
RESULTS

As can be seen from Table 1 all four treatment regimens reduced the incidence of emesis in a pronounced manner. The mean number of emetic episodes during both MCL treatments was 1.3



ANIEMETIC TREATMENT	Loading-infusion	Maintenance-infusion	Total dose per cycle
Metoclopramide I (cisplatin 6 × 60 mg/m^2) 5 × 90 mg/m^2)	0.5 mg/kg/h	0.25 mg/kg/h	7 mg/kg b.w.
Droperidol I (cisplatin 7 × 60 mg/m^2 4 × 90 mg/m^2)	0.05 mg/kg/h	0.025 mg/kg/h	0.7 mg/kg b.w.
Metoclopramide II (cisplatin 5 × 90 mg/m^2) 7 × 120 mg/m^2)	1.0 mg/kg/h	0.50 mg/kg/h	14 mg/kg b.w.
Droperidol II (cisplatin 6 × 90 mg/m^2) 6 × 120 mg/m^2)	0.1 mg/kg/h	0.05 mg/kg/h	1.4 mg/kg b.w.

Fig. 1. Flow sheet of drug protocol.



Figs 2a *and* 2b. *Graphic representations of two-tailed sequential-pair analysis* (15) *of metoclopramide* (*MCL* I *and MCL* II = 7.0 *or* 14 mg/kg b.w. *per cycle*), *and droperidol* (*DRO* I *and DRO* II = 0.7 *or* 1.4 mg/kg b.w. *per cycle*) *as antimetic therapy against cisplatin-induced emesis. MCL* I *was superior in* 10 *of* 12 *and MCL* II *in* 12 *of* 14 *treated pairs* ($\alpha = 0.05$).

Table 1: *Frequency of episodes of vomiting per cycle of cisplatin for the two sequential trials*

	MCL I	DRO I	MCL II	DRO II
	0	3	1	3
	1	4	3	1
	2	2	0	2
	0	1	0	4
	2	5	2	7
	3	0	0	3
	0	3	2	5
	1	2	2	0
	3	4	2	4
	1	3	1	6
	3	5	0	2
	0	2	0	3
			1	3
			0	2
Mean	1.3	2.8	1.0	3.2
Median	1	3	1	3
Range	0–3	0–5	0–3	0–7

(range 0–3) and 1.0 (range 0–3) resp.. The antiemetic potency of DRO was markedly lower, resulting in mean 2.8 (range 0–5) and 3.2 (range 0–7) emetic episodes.

Complete antiemetic protection by MCL was found in 4 of 12 and 6 of 14 patients, resp.. On DRO only one patient in each of the studies was totally protected from emesis. The clinically acceptable and useful result of two or fewer episodes of vomiting was found in 9 of 12 and 13 of 14 (MCL I and MCL II), but in only 5 of 12 and 5 of 14 in the DRO studies.

Nausea was called absent or mild by the majority of the MCL I and MCL II patients (Table 2) and it did not increase markedly immediately prior to emesis. In contrast more than half of the DRO patients classified their nausea as moderate to strong and felt a marked increase before vomiting.

The duration of nausea is listed in Table 3. There is a tendency to longer duration of nausea in both DRO groups compared with the MCL patients.

Table 2. *Self-estimation of nausea and vomiting* (*number of patients per group*)

		None	Mild	Moderate	Strong
Nausea	MCL I	3	5	4	0
	DRO I	1	5	4	2
	MCL II	5	4	4	1
	DRO II	1	4	6	3
Vomiting	MCL I	4	5	3	0
	DRO I	1	4	3	4
	MCL II	6	5	2	1
	DRO II	1	5	5	3

Table 3. Duration of nausea (number of patients per group)

	MCL I	DRO I	MCL II	DRO II
None	3	1	5	1
‹ 6 hr	3	3	3	2
6–12 hr	2	3	3	5
12–24 hr	4	5	2	4
› 24 hr	0	0	1	2

Table 4 shows the frequency of adverse reactions. The incidence of sedation, drowsiness, and extrapyramidal reactions were much more common among the two DRO groups. The incidence of akathisia and/or dystonia was 2.25–2.60-fold higher on DRO than on MCL. For statistical evaluation the two extrapyramidal reactions at the different treatments were grouped into a 2×4 contingency table and submitted to χ^2-test (Hewlett–Packard–41c statistical package): The calculated χ^2 test value for akathisa and/or dystonia was 12.05. The null-hypothesis that there were no differences in the frequency of extrapyramidal reactions could be rejected ($P < 0.05$).

The extrapyramidal reactions required anticholinergic treatment (biperiden 2 mg i.v.) in one patient of MCL I, two of DRO I, one of MCL II, and six of DRO II. During further cytostatic treatment 20 of the 26 patients (77%) on MCL would prefer the same antiemetic treatment whereas 17 of 26 (65%) on DRO would change their antiemetic treatment.

Benefit/risk relationships

In order to quantify the benefit and risk of the different antiemetic interventions the number of prevented emetic episodes (in comparison to the 'nontreatment' of the historical controls, c.f. Methods) was related to the incidence of major side effects, i.e. akathisia and dystonia, or both. The procedure was as follows: the actual mean number of measured emetic episodes of the different groups was subtracted from the expected value of the controls without sufficient treatment, and this difference was used as the numerator. The mean number of extrapyramidal reactions per group was taken as the denominator. The corresponding benefit/risk relationship for the four groups was calculated as follows (c.f. the results given in Tables 1 and 2): MCL I (10.0–1.3) : 0.33 = 26.4; DRO I (10.0–2.8) : 0.75 = 9.6; MCL II (17.1–1.0) : 0.43 = 37.4; DRO II (17.1–3.0) : 1.14 = 12.4.

Table 4. Adverse reactions per drug and drug dosage (number of patients per group)

	MCL I	DRO I	MCL II	DRO II
Number of total patients	12	12	14	14
Akathisia	3	6	5	10
Dystonia	1	3	1	6
Rigor	3	5	3	9
Sedation	5	6	8	10
Drowsiness	3	5	3	7

DISCUSSION

The results of these two sequential trials show that both drugs at the doses used are effective antiemetics against different doses of cisplatin. However, MCL was significantly more effective than DRO in the sequential comparisons, resulting in 2–3-fold lower incidence of cisplatin-induced vomiting. Furthermore, duration of nausea, self-estimation of nausea and vomiting, and drug preference, was clearly in favour of MCL. These results are in accordance with those of Lewis *et al.* [16] who studied DRO and MCL at comparable dosage, but shorter duration of treatment. High antiemetic protection by DRO has recently been reported in a preliminary dose-finding study at total doses of 67.5 mg per cycle [17]. Different studies at various lower doses of DRO appear to be definitely less effective [4, 18] in comparison with our present results.

The incidence of extrapyramidal side effects was significantly higher in the DRO groups compared with the MCL groups. Similar results have been obtained previously in a study comparing MCL with the neuroleptic butyrophenone haloperidol [19]. The differences in the antiemetic and extrapyramidal effects of DRO vs. MCL may be due to a relatively selective affinity of MCL to a dopamine receptor subtype at the chemoreceptor trigger zone [20], whereas DRO appears to possess a relatively higher affinity to nigrostriatal dopaminergic receptors [21]. Cisplatin has not only central effects on the chemoreceptor trigger zone [20] but also a marked peripheral action [10]: it relaxes the smooth muscle tone in the gastrointestinal tract including the lower esophageal sphincter and may cause antiperistalsis. It has been shown that MCL can enhance the diminished gastrointestinal motility and reverse the antiperistaltic action of cisplatin [10]. This contributes to the antiemetic potency of MCL against cisplatin. In contrast, no clinical relevant effect on gastrointestinal motility has been observed for DRO *in vitro* or *in vivo* [22, 23]. The peripheral mechanism of action of MCL has been attributed to a partial agonistic activity on serotoninergic interneurons of the gastrointestinal smooth muscle rather than to peripheral dopaminergic receptor interactions [24].

The difference centralnervous and peripheral receptor affinities of MCL in comparison to DRO may explain the threefold better benefit/risk relationship of MCL. It follows from our results that MCL should be preferred in the routine management of cisplatin-induced emesis.

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