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Antiemetic Efficacy of High-Dose Dexamethasone: Randomized, Double-Blind, Crossover Study with High-Dose Metoclopramide in Patients Receiving Cancer Chemotherapy

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Abstract—*A double-blind, randomized, crossover study was conducted to compare the efficacy and safety of high-dose dexamethasone and high-dose metoclopramide in the treatment of chemotherapy-induced nausea and vomiting. All entered patients had no prior chemotherapy and all received inpatient emetogenic chemotherapy mainly without cisplatin. Of the* 40 *evaluable patients,* 23 (58%) *had no vomiting with dexamethasone compared with only* 11 (28%) *receiving metoclopramide* ($P < 0.025$). *Dexamethasone was found to have less adverse effect than metoclopramide on patient's appetite and activity* ($P < 0.025$ *and* $P < 0.01$, *respectively*). *Twenty-one patients* (53%) *developed mild to severe somnolence with metoclopramide compared to only seven* (18%) *who experienced this adverse effect with dexamethasone* ($P < 0.01$). *Six patients* (15%) *developed extrapyramidal manifestations with metoclopramide, but none with dexamethasone. Furthermore, during dexamethasone therapy, patients developed less diaphoresis, insomnia, headache and dizziness. Upon questioning patients about their preference to future use of the antiemetic drug therapy,* 28 *patients* (70%) *preferred dexamethasone, two* (5%) *preferred metoclopramide and* 10 (25%) *found no difference. We conclude that high-dose dexamethasone has a greater antiemetic activity and is more safe than high-dose metoclopramide in patients receiving emetogenic chemotherapy mainly without cisplatin.*

INTRODUCTION

NAUSEA and vomiting are frequent and serious complications of cancer chemotherapy [1–3]. Fear of these side effects can result in many patients rejecting treatment with potentially curative or highly palliative chemotherapy. Total protection or adequate control of chemotherapy-induced nausea and vomiting is of essential importance to improve patients acceptance of anticancer therapy.

Various groups of antiemetics with variable modes of action and variable success rates have been used [4–6]. Metoclopramide, a procainamide derivative has both central and peripheral antiemetic properties [7, 8]. When given in conventional doses, metoclopramide was found generally to be ineffective [6, 9]. However, using the drug in high-doses, has recently been shown to possess significant antiemetic activity. This has been particularly true against cisplatin-induced nausea and vomiting [10–13].

Dexamethasone and methylprednisolone have been shown to be more effective than placebo [14], and possibly superior to phenothizines in controlling emesis produced by potent emetogenic drugs [15]. Major antiemetic response of 70–80% have been demonstrated with their use [14–19]

This double-blind, randomized, crossover trial, was initiated to compare the antiemetic efficacy of high-dose dexamethasone with high-dose metoclopramide in patients who are mainly receiving non-cisplatin emetogenic chemotherapy.

MATERIALS AND METHODS

From September 1984 to January 1985 patients with histologically confirmed cancers receiving inpatient chemotherapy for the first time were subjected to the study. Only those who had a performance status of 70% or more on the Karnofsky, were included. We excluded from the trial, patients above the age of 70, patients who had anticipatory vomiting before chemotherapy, and those who had

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absolute or relative contraindications to the use of steroids. A written informed consent was obtained from all patients participating in the study.

A randomized, double-blind, crossover design was used in which each patient served as his or her own control. While patients were randomly assigned, a balanced assignment between the two arms was maintained throughout the study. During two consecutive courses of the same chemotherapeutic regimen in the same dosage, each patient was randomly assigned to receive either high-dose metoclopramide or high-dose dexamethasone, and during the second course of chemotherapy, the patient received the alternate treatment regimen.

Metoclopramide was given as an intravenous piggyback over a 15-min period as 1 mg/kg for five doses beginning 30 min before chemotherapy, and at 1.5, 3.5, 5.5 and 8.5 hr after the initiation of chemotherapy. Dexamethasone 20 mg was administered as an intravenous piggyback over a 15-min period beginning 30 min before chemotherapy and 10 mg at 1.5, 3.5, 5.5 and 8.5 hr after chemotherapy.

Only clear fluids by mouth were allowed during the initial 12 hr of the trial, and no other drugs or antiemetics were given 24 hr before or after the start of chemotherapy regimen.

Prior to the administration of each arm of the study, each patient was assessed for his or her baseline status in the 24-hr period before chemotherapy. Treatment was postponed if normal baseline status was not established. Both the patient and the person evaluating the patient's response were blinded from the identity of the given antiemetic. In addition to the baseline evaluation, each patient was evaluated 24 hr after the chemotherapy administration.

Nausea was graded as follows: 0 (none), 1 (mild, no interference with activity). 2 (moderate–severe, interference with activity). Vomiting was graded according to the number of emetic episodes: 0 (none), 1 (mild, fewer than 5), 2 (moderate–severe, more than 5). Activity during the trial was graded as follows: 0 (normal activity), 1 (mild impairment of activity), 2 (moderate impairment of activity), 3 (severe, bedridden for more than 2 hr because of symptoms). The patient's appetite was also graded as follows: 0 (normal appetite), 1 (mild impairment due to symptoms), 2 (moderate–severe impairment due to symptoms), 3 (appetite increased). Any sedative effect of antiemetic was evaluated according to the following grades: 0 (none), 1 (mild, lethargic, arousable by verbal stimuli, completely oriented), 2 (severe, arousable only by physical stimuli but disoriented). Patients were assessed for the side effects of antiemetics such as : chills, diaphoresis, headache, dizziness, hypotensive symptoms, ataxia, hallucinations, euphoria, extrapyramidal manifestations or any other symptoms. After the second antiemetic, patients were asked about their preference to which antiemetic they would like to receive with their future therapy. Only after the second part of the trial was the identity of the antiemetic revealed.

In the statistical analysis of the study, the chi-square test of homogeneity was used to evaluate independent samples. McNemar's test [20], was used to evaluate paired data.

RESULTS

Forty-three patients were randomly assigned with a balanced entry to the two arms of the study. Three patients were excluded after receiving only one antiemetic for the following reasons: two patients refused in-patient therapy for social reasons (both had dexamethasone), the third developed disease progression and therapy was changed (had metocolpramide). The remaining 40 patients were evaluable for antiemetic response. The characteristics of the evaluable patients are shown in Table 1. The various chemotherapeutic agents and drug combinations used were classified into three groups using a modified classification from that proposed by Sallen and co-workers [21]. Table 2 shows the drug classifications and the number of patients in each class.

Table 3 demonstrates the antiemetic response to dexamethasone and metoclopramide. While 19 patients (48%) did not experience nausea with dexamethasone, only 11 patients (28%) had no nausea during metocolpramide therapy. The difference was suggestive but was not statistically significant ($0.05 < P\text{-value} < 0.1$). Twenty-three patients (58%) achieved complete antivomiting protection with dexamethasone compared to 11 patients (28%) with metoclopramide (P-value < 0.025).

Both dexamethasone and metoclopramide were evaluated for their potential side effects. Table 4 demonstrates the sedative effect as well as the effect of both antiemetics on activity and appetite. In comparison with metocolpramide, dexamethasone has produced less somnolence (P-value < 0.01). Metocolpramide had more adverse effect on activity and appetite compared to dexamethasone ($P < 0.01$ and $P < 0.025$ respectively). Table 5 compares the side effects of both drugs. Extrapyramidal side effects of high-dose metocolpramide occurred in six patients (15%). Two patients developed torticollis, two developed akathisis which manifested itself as restlessness, one patient developed trismus, and the sixth developed urinary retention. All extrapyramidal manifestations responded promptly to 50 mg IV or IM of diphenhydramine. While 21 patients (53%) did not develop any side effects with dexamethasone, only 10 (25%) had no side effects with metocolpramide use ($P < 0.005$).

Table 1. *Characteristics of the* 40 *evaluable patients*

No. of patients	40
Age in yr	
Median	39
Range	(17 – 67)
Performance status	No. of patients
70–80%	17
80–90%	13
90–100%	10
Type of cancer	No. of patients
Non-Hodgkin's lymphoma	13
Hodgkin's disease	9
Breast	6
Gastric	5
Ovarian	3
Hepatoma	2
Sarcoma	2

Table 2. *Classifications of chemotherapeutic agents according to their emetogenic activity*

	No. of patients (%)
A. Greatest emetogenic activity: Combinations of agents including cisplatin*, doxorubicin, cyclophosphamide (> 1000 mg/m^2), or nitrogen mustard	24 (60%)
B. Moderate emetogenic activity: Combinations of agents including high-dose methotrexate, actinomycin-D, doxorubicin, cyclophosphamide (< 1000 mg/m^2), or mitomycin-C	14 (35%)
C. Least emetogenic activity: Single agents including high-dose methotrexate, cyclophosphamide and doxorubicin	2 (5%)

*Only two patients had cisplatin-containing combinations.

Table 3. *Antiemetic response to dexamethasone and metoclopramide*

		*Metoclopramide Degree of nausea**			
		0	1	2	Total
Dexamethasone Degree of nausea	0	9	7	3	18
	1	4	7	7	18
	2	0	2	1	3
	Total	13	16	11	40

$X^2_3 = 6.596$

$0.05 < P\text{-value} < 0.1$

		Metoclopramide Degree of vomiting†			
		0	2	3	Total
Dexamethasone Degree of vomiting	0	7	9	7	23
	1	4	7	4	15
	2	2	1	1	2
	Total	11	17	12	40

$X^2_3 = 10.723$

$P < 0.025$

* Nausea: 0 (non), 1 (mild, no interference with activity), 2 (moderate-severe, interference with activity).

†Vomiting: 0 (none), 1 (mild, fewer than 5 episodes), 2 (moderate-severe, more than 5 episodes).

Each cell represents the point response of the patients to dexamethasone and metoclopramide. For example, with respect to nausea nine patients had no nausea to both drugs, whereas seven had no nausea to dexamethasone but mild nausea to metoclopramide.

Regarding patients's preferences, 28 patients (70%) preferred dexamethasone, two (5%) preferred metoclopramide, and 10 (25%) found no difference.

No significant correlation was found between the antiemetic response and patients's age, sex, or the emetogenic chemotherapy class.

The effect of order was studied for both used antiemetics. The sequence of use of dexamethasone did not influence its antinausea or antivomiting effects (chi-square = 0.6082 and 2.1101 respectively). The order was also found to have no influence on the antinausea or antivomiting effects of metoclopramide (chi-square = 1.1451 and 0.1497). Furthermore, the degree of nausea or vomiting did not vary significantly between the first and second cycles of therapy irrespective of the antiemetic used.

DISCUSSION

In this double-blind, crossover, randomized study, we have shown that high-dose dexamethasone is an effective antiemetic drug. Complete antinausea and antivomiting protection was achieved in 19 (48%) and 23 (58%) patients respectively. While the antivomiting effect of dexamethasone was clearly superior to metocolpramide, its antinausea superiority was only suggestive. This difference, in our view, could be partially related to the subjective nature of nausea. Although nausea and vomiting are closely correlated in other studies, this was not clearly demonstrated in our own.

The study has also demonstrated the safety of the dexamethasone regimen compared to the high-dose metocolpramide. Dexamethasone had no adverse effect on the activity of 35 patients (88%), or the appetite of 31 (78%). Only six patients (15%) experienced mild sedation with dexamethasone, in contrast to 21 patients (53%) who developed mild to severe somnolence with metocolpramide. The high incidence of extrapyramidal manifestations in 15% of patients was similar to that found in other studies [10, 22].

Due to the efficacy as well as safety of high-dose

Table 4. Side effects of metoclopramide and dexamethasone

Effect on activity Metoclopramide*

Dexamethasone	0	1	2	3	Total
0	18	6	10	2	36
1	0	2	0	0	2
2	0	0	1	0	1
3	0	1	0	0	1
Total	18	9	11	2	40

$X_6^2 = 18$

$P < 0.01$

Effect on appetite† Metoclopramide

Dexamethasone	0	1	2	Total
0	17	10	4	31
1	2	3	1	6
2	0	0	3	3
Total	19	13	8	40

$X_3^2 = 10.33$

$P < 0.025$

Somnolence‡ Metoclopramide

Dexamethasone	0	1	2	Total
0	18	14	1	33
1	1	6	0	7
2	0	0	0	0
Total	19	20	1	40

$X_3^2 = 12.267$

$P < 0.01$

*Activity: 0 (normal), 1 (mild impairment), 2 (moderate impairment), 3 (severe impairment, bedridden > 2 hours)

†Appetite: 0 (normal), 1 (mild impairment), 2 (moderate-severe impairment).

‡Somnolence: 0 (none), 1 (mild), 2 (severe).

dexamethasone, the drug was clearly preferred by 70% of patients.

The antiemetic potentials of dexamethasone and metoclopramide were compared in few limited clinical trials [23–25]. In one of these clinical trials [25], high-dose dexamethasone was found to be a more effective antiemetic than high-dose metoclopramide and was preferred by the patients treated. High-dose metoclopramide was found to be effective in controlling nausea and vomiting in regimens employing cisplatin [13]. In our study, while 24 patients received various drug combinations of high emetogenic potentials, only two had cisplatin-containing regimens. Due to this fact the efficacy of high-dose dexamethasone against cisplatin could not be tested. The antiemetic potential as well as the safety of dexamethasone in this trial suggests an effective protective action against potent emetogenic drugs.

The efficacy that was demonstrated in our study of high-dose dexamethasone over high-dose metoclopramide could not be attributed to the dose of metoclopramide used. While a dose–response relationship for metoclopramide has been demonstrated, mainly, against cisplatin-induced emesis [13], variable dose regimens have achieved adequate antiemetic responses. Metoclopramide given intravenously as 2 mg/kg for five doses, was found to be more effective than prochlorperazine in patients treated with high-doses of cisplatin [11]. A lower dose of 1 mg/kg for a total of six doses was found to be effective in patients treated with moderate dose of cisplatin when used in combination with other potentially emetogenic chemotherapeutic agents [12]. Furthermore, lower dose schedule of 20 mg intravenously for six doses was found to be equally effective to 0.75 mg/kg intravenously for six doses in patients receiving non-cisplatin emetogenic drugs [22]. On the other hand, in most studies, metoclopramide's side effects were primarily related to the used dose. In our study, higher dose schedule would have produced higher

Table 5. Side effects of metoclopramide and dexamethasone

Side Effect	Metoclopramide		Dexamethasone		P-Value
	Yes	*No*	*Yes*	*No*	
Hallucinations	2	38	—	40	NS*
Chills	5	35	2	38	NS
Euphoria	—	40	2	38	NS
Diaphoresis	16	24	5	35	$P<0.005$
Extrapyramidal	6	24	—	40	$P<0.025$
Insomnia	14	26	5	35	$P<0.025$
Headache	19	21	9	31	$P<0.025$
Dizziness	26	14	7	33	$P<0.005$

*NS = Not significant.

incidence of unacceptable toxicity.

The optimal dose and schedule for dexamethasone is yet to be determined. The high-dose dexamethasone regimen employed in our study, was almost equal to doses used mainly orally in other clinical trials [19, 25]. On the other hand, smaller dose regimens have been used effectively against non-cisplatin containing emetogenic chemotherapy [14]. A relative lack of dose–response relationship for dexamethasone was noted by Drabkin *et al.* in patients receiving cisplatin [26]. In the later study, 17 of 22 patients had no apparent benefit by escalating the dexamethasone dose.

The possible adverse effects of corticosteroids on the immune system cannot be ignored [27, 28]. However, those effects are primarily related to its prolonged use rather than to the short and intermittent exposure.

Another area of concern in association with the use of steroids in cancer patients is the possible interferance with the antitumour potentials of chemotherapeutic agents. The combination of prednisolone with high-dose cyclophosphamide has produced inferior results compared to high-dose cyclophosphamide alone in patients with metastatic lung cancer [29]. While the number of patients in the later study was rather small, a possible interferance with the rate of metabolic biotransformation of cyclophosphamide induced by prednisolone could have accounted for the inferior results. On the other hand, data derived from animal models regarding this action are somewhat conflicting [30, 31]. Furthermore, the available data for the antidrug effect of corticosteroids on chemotherapeutic agents in man are not convincing.

The major drawback of our dexamethasone regimen is the length of therapy and necessity for its inpatient administration. The results derived from the study clearly demonstrate the significant antiemetic properties of high-dose dexamethasone and its safety compared to high-dose metoclopramide. However, further studies investigating dexamethasone schedule and dosage to be more suitable for outpatient use are needed.

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