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Randomized Open Cross-over Trial between Metoclopramide (MCP) and Dexamethazone (DXM) for the Prevention of Cisplatin-induced Nausea and Vomiting*

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Abstract—*Thirty-five patients receiving chemotherapeutic regimens including cisplatin (CDDP) were entered into a randomized open cross-over trial. Sixteen patients had previously received chemotherapy. Metoclopramide (MCP) was given i.v. in 4 doses of* 1 mg/kg *over a period of* 4½ hr, *dexamethazone (DXM) was administered i.m. in 4 doses of* 8 mg *over* 24 hr *and another* 10 mg *i.v. just prior to CDDP administration. Sixteen patients who expressed a positive opinion on both previous antiemetics were given placebo (PLC). No significant differences were found between MCP and DXM, considering the mean score of both emesis intensity and patient's opinion. The mean duration of the symptoms was significantly longer with MCP than with DXM* ($P < 0.02$). *Both antiemetic agents were more effective than PLC. No significant side-effects were observed. The results of this study indicate that both MCP and DXM provide a similar protection against CDDP-induced nausea and vomiting.*

INTRODUCTION

NAUSEA and vomiting are frequent symptoms in patients receiving chemotherapy. In some cases, patients refuse to continue a potentially effective treatment because of the severity of these side-effects. The activity of the traditional antiemetics such as phenothiazines is often variable and incomplete [1–5]. Cisplatin (CDDP) is one of the most emetic of the cytotoxic drugs employed in cancer chemotherapy.

High intravenous doses of metoclopramide (MCP) (1–2 mg/kg administered 5–6 times) have recently been shown to be active in cisplatin-induced nausea and vomiting [6–8]. This drug, a derivative of procainamide, exerts its antiemetic effects both by blocking neuroreceptors in the chemoreceptor trigger zone, located near the fourth ventricle in the 'area postrema', and by stimulating gastric and small bowel motility, thus preventing gastric stasis and dilatation, which are a part of the vomiting reflex [9–11]. When administered in standard doses, however, MCP has generally given conflicting results in preventing nausea and vomiting [12–14].

Preliminary reports have demonstrated that corticosteroids, administered at high doses, can also prevent these symptoms [15–18]. A possible mechanism of action could be interference with prostaglandin release [15], although more recent reports do not confirm this hypothesis [19].

This report presents the results of a randomized open cross-over trial comparing the administrations of high doses of MCP with dexamethasone (DXM) to patients treated with a 2-drug combination including CDDP.

MATERIALS AND METHODS

Between January and July 1982, 35 outpatients were entered into this trial. Subjects with diabetes mellitus, peptic ulcers or moderate or severe hypertension were not included. The study was carefully explained to the patients and informed consent was obtained. Twenty-two were male and 13 female (median age, 59 yr; range, 31–75 yr).

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Sixteen patients (45.7%) had previously received chemotherapy and 9 patients (25.7%) had already received cisplatin. Thirty had squamous cell carcinoma of the head and neck and 5 had ovarian carcinoma. Those with head and neck squamous cell carcinoma received the CABO combination (cisplatin, methotrexate, bleomycin and vincristine) and cisplatin alone on the day that they were given the antiemetics. The patients with ovarian carcinoma received the PAC combination (cisplatin, adriamycin and cyclophosphamide) and adriamycin (40 mg/m^2) with cisplatin on the day that they received the antiemetics. Cisplatin was administered in both regimens at a dosage of 50 mg/m^2) every 3 or 4 weeks according to Vogl *et al.*s [20] regimen of hydration and forced diuresis. This drug was administered i.v. 30 min after starting a 2-hr infusion of 2 l of 5% dextrose in a 0.45% saline with 10 mEq of KCl/l, 40 mg of furosemide were given i.v. at the start of the infusion and 12.5 g of mannitol i.v. prior to cisplatin administration.

MCP was given at a dosage of 1 mg/kg i.v., 30 min before and 1, 2 and 4 hr after cisplatin; DXM at a dosage of 8 mg i.m., 24 and 12 hr before and 6 and 12 hr after cisplatin; and 10 mg of DXM were given intravenously just prior to cisplatin administration. The first antiemetic that the patient received was randomly DXM or MCP and the second was automatically the other agent, so that each patient was used as his own control. The patients were requested not to eat after dinner on the day prior to treatment, nor was food or drink permitted during the initial 12 hr of the treatment. At the end of the CDDP treatment the patients completed a questionnaire in which they rated their nausea and vomiting on a scale of 0–4 (0: no side-effect; 1: only nausea; 2: mild vomiting, less than 5 episodes; 3: severe vomiting, 5–15 episodes; 4: intolerable vomiting, more than 15 episodes). The patients were also asked to record the onset and end of nausea and vomiting. Duration was then calculated as the interval between the two recordings. They were also asked to express their overall opinion on a semantic scale (good = 1; fairly good ± 2; bad = 3; very bad = 4). When the questionnaires were collected the patients were interviewed by a member of the research team regarding the side-effects caused by the antiemetic drugs and the questionnaires were reviewed and, if necessary, clarified.

During the third course of CDDP, placebo (PLC) was given to patients who had expressed a positive opinion (good or fairly good) on previous antiemetics and droperidol (DRP) to those with a negative opinion (bad or very bad), the latter at a dosage of 2.5 mg diluted in the first and in the fourth 500 ml of the 2-l infusion.

Statistical analysis

The differences of emesis intensity and the patients' overall opinions between the two antiemetic treatments were evaluated with Student's t test and the differences in distribution of patients regarding the degrees of emesis with the Kolmogorov–Smirnow test [21]. The Fisher exact test was used to evaluate the differences in nausea and vomiting duration. A single value (calculated as duration in min × degree of nausea and vomiting) was used to standardize these variables, employing the Mann–Whitney non-parametric U test because of the skew distribution of obtained values. The McNemar test was used to assess the differences between expected and observed opinion of the patients.

RESULTS

All the patients completed at least two courses of chemotherapy so that their response to MCP and DXM could be properly evaluated. Nine patients (25.7%) receiving MCP and 7 (20%) receiving DXM had complete relief from nausea and vomiting. Twenty-six out of 35 (74.3%) with MCP and 22 (62.9%) with DXM had no symptoms, only nausea or less than 5 episodes of vomiting (0–1–2 intensity score). No statistically significant differences between the two antiemetic treatments were found among the 5 subgroups using the Kolmogorov–Smirnow test. As Fig. 1 shows, no significant differences were found

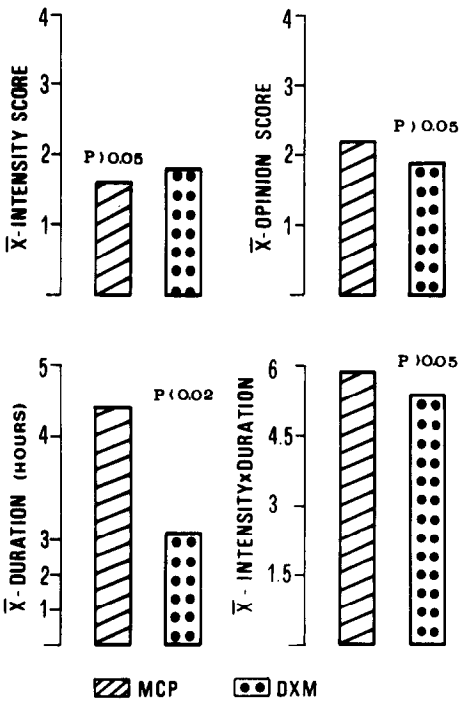

Fig. 1. Antiemetic effects in 35 patients treated with MCP and DXM. X̄ = mean; MCP = metoclopramide; DXM = dexamethazone.

between MCP and DXM considering the mean score of intensity (MCP, 1.56, DXM, 1.87, $P > 0.05$) and the mean score of the patients' opinion (MCP, 2.15, DXM, 1.96, $P > 0.05$). The mean duration of symptoms was significantly longer for MCP than for DXM (MCP, 4.42 ± 1.21 hr, DXM, 3.11 ± 0.66 hr, $P < 0.02$). The sequence of administration of the two drugs did not influence the results, regarding mean score of both intensity (MCP + DXM = 3.56; DXM × MCP = 3.31, $P > 0.05$) and opinion (MCP + DXM = 4.25, DXM + MCP = 4.00, $P > 0.05$). The mean time of the onset of symptoms was 2.97 hr for MCP and 2.88 hr for DXM. No statistically significant differences between the two treatments were found when comparing the products between intensity score and duration in min (MCP = 597, DXM = 502, $P > 0.05$).

To evaluate the influence of prior chemotherapy we compared results between patients previously treated and those untreated. For each objective parameter of evaluation (intensity, opinion and duration) we calculated the sum of the variables obtained with MCP and DXM. Patients who had previously received chemotherapy were less responsive to the antiemetic drugs regarding both mean intensity score (4.44 vs 2.74, $P = 0.05$) and mean duration (10.55 vs 4.96 hr, $P = 0.05$). The differences were found mainly with MCP treatment (mean intensity scores, $P = 0.001$; mean duration, $P = 0.01$), while no significant differences were found with DXM ($P > 0.2$).

Ten out of 35 patients (28.6%) expressed an opposing opinion regarding the two antiemetics: 2 (5.7%) a positive opinion of MCP and 8 (22.9%) a positive opinion of DXM. Twenty-five out of 35 patients (71.4%) expressed a homologous opinion opinion of both the antiemetic treatments: 20 (57.1%) positive and 5 (14.3%) negative.

Only 21 out of 25 patients received a third antiemetic during the third course of CDDP. Sixteen patients received PLC and 5 were given DRP. The remaining 4 changed their chemotherapy after 2 courses because of disease progression. MCP and DXM were significantly more active than PLC in the 16 patients treated, considering the intensity score (MCP = 0.87, PLC = 2.31, $P < 0.05$; DXM = 1.19, PLC = 2.31, $P < 0.05$), mean opinion score (MCP = 1.44, PLC = 2.50, $P < 0.05$; DXM = 1.56, PLC = 2.50, $P < 0.05$) and mean duration of symptoms (MCP = 0.61 hr, PLC = 2.71 hr, $P < 0.05$; DXM = 0.85 hr, PLC = 2.71 hr, $P < 0.05$).

The 5 patients submitted to DRP did not respond and emesis duration was significantly longer (24 hr) than with MCP (9.8 hr). No severe side-effects were observed from MCP and DXM treatment. Mild-to-marked sedation (42.8% of the patients) occurred after MCP treatment. Dry mouth (22.9%), muscular weakness (11.4%) and anxiety (8.6%) were also reported. No extrapyramidal reactions were observed. DXM-related side-effects were facial erythema and euphoria (8.6%), urticaria, pyrosis and mild hyperglycemia (2.9%). Of the five patients receiving DRP, 4 had marked sedation, 2 dry mouth and dizziness and 1 orthostatic hypotension.

DISCUSSION

This report is the first trial comparing antiemetics MCP and DXM. The results of this study indicate that at the dosage employed, the two drugs provide a similar protection against cisplatin-induced nausea and vomiting. Our experimental trial was designed to rule out several variables which could interfere with a proper interpretation of studies on antiemetic drugs. All the patients received cisplatin at the same dosage (50 mg/m^2) and regimen. Only 5 patients also received adriamycin (40 mg/m^2) on the day that they were given the antiemetics, but they, too, were sequentially submitted to both antiemetics and used as their own controls. The design of the study was considered the most reliable for evaluating the effectiveness of antiemetic agents.

The effect of PLC or individual resistance to emetics was sought only in patients who had thought positively of the two previously administered antiemetic treatments. We obviously continued the more effective agent on those patients who expressed a reverse opinion on previous experiences and administered droperidol, a third antiemetic drug, to patients previously resistant to both.

Cisplatin is one of the most emetic of the cytotoxic drugs used in cancer chemotherapy [22], confirmed by results of placebo treatment (Fig. 2). A peripheral pathway has been suggested as the most likely mechanism [23] and could account for the high MCP activity in cisplatin-induced emesis [6–8].

To date, the optimal dosage and schedule of MCP has not yet been fully investigated. The high-dose regimen proposed by Gralla *et al.* [6] is, in fact, not suitable for outpatients because of the length of treatment, and could be an overload for patients receiving lower doses of CDDP [3, 8]. The lower cumulative dosage (4 mg/kg) and the shorter course of our regimen (4 doses over 4.5 hr) enabled this therapy to be administered on an outpatient basis, still maintaining the antiemetic efficacy (Fig. 2).

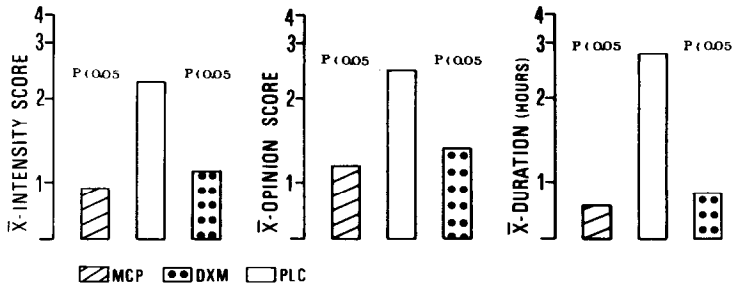

Fig. 2. Antiemetic effects in 16 patients treated with PLC after MCP and DXM admininistration (see text). $\bar{X}$ = mean; MCP = metoclopramide; DXM = dexamethazone; PLC = placebo.

Considering the conditions of the patients, it is difficult to accurately establish the relationship between the effectiveness of the antiemetic drugs and the opinion of the patients. On the basis of emesis intensity and duration, we calculated a hypothetical expected opinion which was then compared to that actually observed. In fact, the opinions of the patients were worse than what we had predicted for both MCP ($P = 0.0005$) and DXM ($P = 0.01$). Other authors have observed that the only important endpoint related to the patients' opinions is complete control of vomiting [24]. Once the patient develops emesis, objective parameters of evaluation often differ from the patients' opinions; we cannot provide a reliable explanation for this phenomenon.

The side-effects caused by MCP were mild and acceptable. DXM can safely be administered at the dosages reported whenever corticosteroids are not contraindicated.

These results, however, are to be considered preliminary findings requiring further confirmation from more trials that include a larger number of patients. Studies on dexamethasone and other corticosteroids are currently in progress to establish the optimal dosage and schedule, either alone or in combination with other regimens, for controlling vomiting in cancer patients.

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