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Short communication

Antiemetic activity of high-dose methylprednisolone associated with continuous-infusion metoclopramide and oral alprazolam during multiple-day chemotherapy

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Summary. The addition of high-dose methylprednisolone (120 mg given i.v. and repeated after a 4-h interval) to a conventional antiemetic regimen consisting of metoclopramide (0.5 mg/kg given as an i.v. bolus over 30 min followed by 1 mg/kg given as a continuous infusion over 24 h) and alprazolam (0.5 mg given p.o.) was evaluated in a randomized study of leukemic patients undergoing anthracycline-containing multiple-day chemotherapy. Double-blind analysis was done in 30 patients who completed a total of 40 treatment courses. Cumulative 3-day results revealed complete control of nausea in 66% of patients and complete control of emesis in 77% of cases. The addition of methylprednisolone significantly reduced the occurrence of nausea ($p = 0.003$) and emesis ($P = 0.06$). Moreover, antiemetic rescue with chlorpromazine was less frequently necessary in patients receiving corticosteroids ($P = 0.02$). No harmful side effect was observed, and the incidence of severe infectious episodes was similar in both arms. We conclude that high-dose methylprednisolone can improve the efficacy of metoclopramide and alprazolam in controlling nausea and emesis induced by anthracycline-containing multiple-day chemotherapy in patients with acute myeloblastic leukemia.

Introduction

Nausea and vomiting create considerable discomfort for cancer and leukemic patients undergoing chemotherapy. Preventive therapy is based on the administration of phenothiazine or benzamide as either a bolus injection or a continuous infusion [4, 10, 11]. A benzodiazepine is usually given to reduce the anxiety of the patient [3]. High-dose corticosteroids, such as methylprednisolone and dexamethasone, have demonstrated their usefulness in controlling nausea and vomiting when given either alone or in combination with anticancer drugs [1, 2, 7, 9]. However, most studies of these regimens have involved cisplatin-containing single-day chemotherapy. Multiple-day combination chemotherapy containing either antracyclines or anthracenedione and cytosine arabinoside, such as that used in the treatment of acute myeloblastic leukemia (AML), also induces severe nausea and vomiting [8], but few data are available concerning the efficacy of antiemetic regimens given over several days. The aim of the present randomized, double-blind study was to analyze the efficacy of high-dose methylprednisolone given in adjunct with continuous-infusion metoclopramide and oral alprazolam in preventing nausea and emesis in adult patients receiving a 3-day anthracycline/anthracenedione regimen for treatment of AML.

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Patients and methods

Patients. From January to July 1990, 30 consecutive patients (median age, 49 years; range, 17–81 years) admitted in the intensive care unit of our department for treatment of AML (at diagnosis or in relapse) with a multiple-day anthracycline- or anthracenedione-containing chemotherapy regimen were included in this study. Patients presenting with extrapyramidal symptoms, previous psychotic episodes, or severe diabetes mellitus were excluded from the study.

Chemotherapy regimen. All patients received combination chemotherapy including 3 days of daunorubicin (30–80 mg/m^2 per day, 25 cases) or mitoxantrone (8–12 mg/m^2 per day, 15 cases) and 6–7 days of continuous-infusion cytosine arabinoside (100–500 mg/m^2 per day). Daunorubicin and mitoxantrone were given as 30-min infusions. Characteristics of the 40 chemotherapy courses completed by 30 patients (10 subjects were randomized twice at a minimal 3-month interval) are described in Table 1.

Antiemetic protocol. Over the 3 days of daunorubicin or mitoxantrone therapy, all patients received metoclopramide (0.5 mg/kg given as an i.v. bolus plus 1 mg/kg given as a 24-h continuous infusion) and alprazolam (0.5 mg daily p.o.). Methylprednisolone (MP, 120 mg given i.v. before chemotherapy and repeated 4 h later) was given randomly during the same period in 20 of 40 courses (arm A, without MP; arm B, with MP). Additional chlorpromazine (12.5 mg q 6 h) was given as rescue treat-

Table 1. Characteristics of patients included in the study

	Total (*n*)	Arm A (*n*)	Arm B (*n*)
Chemotherapy courses	40	20	20
Median age (range)	49 (17–81) years	54 (20–81) years	44 (17–78) years
Men/women	17/23	8/12	9/11
Number of chemotherapy courses received during the previous 6 months:			
0	26	16	10
⩾1	14	6	8
Treatment:			
Daunorubicin, e50 mg/m^2 per day	5	3	2
Daunorubicin, f70 mg/m^2 per day	20	11	9
Mitoxantrone, 8 mg/m^2 per day	4	2	2
Mitoxantrone, 12 mg/m^2 per day	11	4	7

Table 2. Comparison of results obtained in 20 patients who were treated with metoclopramide and alprazolam alone (arm A) versus those achieved in 20 patients who were treated with metoclopramide, alprazolam and methylprednisolone (arm B)

	Arm A	Arm B	*P* value if ≤0.1 (Fisher)
Day 1:			
Patients without nausea (%)	7 (35)	12 (60)	0.1
Patients without emesis (%)	11 (55)	13 (65)	NS
Chlorpromazine rescue (%)	3 (15)	0 (0)	NS
Day 2:			
Patients without nausea (%)	13 (65)	17 (85)	NS
Patients without emesis (%)	15 (80)	18 (90)	NS
Chlorpromazine rescue (%)	4 (20)	2 (10)	NS
Day 3:			
Patients without nausea (%)	12 (60)	18 (90)	0.03
Patients without emesis (%)	15 (75)	19 (95)	0.09
Chlorpromazine rescue (%)	4 (20)	2 (10)	NS
Total over 3 days:			
Absence of nausea:			
Number of patients (%)	5 (25)	12 (60)	0.03
Number of days (%)	32 (53)	47 (78)	0.003
Absence of emesis:			
Number of patients (%)	8 (40)	16 (65)	NS
Number of days (%)	42 (70)	50 (83)	0.06
Chlorpromazine rescue:			
Number of patients (%)	5 (25)	3 (15)	NS
Number of days (%)	11 (18)	4 (7)	0.02
Adverse events during chemotherapy:			
Severe infections (%)	9 (47)	5 (25)	NS
Fungal infections (%)	3 (18)	0 (0)	0.09
Death (leukemia and toxic) (%)	5 (25)	1 (5)	0.09

NS, Not significant

ment when patients experienced severe uncontrolled nausea or vomiting, regardless of the arm allocation.

Evaluation of results. The number of vomiting episodes and the duration of nausea were recorded every day by each patient with the assistance of a person who had no knowledge of the arm allocation of the patient. Severe infectious episodes and deaths were recorded after the resolution of therapeutic aplasia.

Statistics. Statistical analyses were performed using Fisher's two-tailed exact test.

Results

Overall results

Over the 3 days of treatment, complete protection from nausea was achieved in 66% of patients and complete protection from vomiting, in 77% of cases. The complete protection of patients increased from day 1 to day 3 for nausea (from 47% to 75%; $P = 0.1$) and for vomiting (from 60% to 85%; $P = 0.01$), but the prescription of chlorpromazine also increased slightly (from 7.5% to 15%; $P = 0.24$). There were no differences in the incidence of nausea and vomiting according to sex (nausea, 31% in men and 33% in women; vomiting, 24% and 23%, respectively; chlorpromazine rescue, 10% and 12%, respectively). The type of intercalating agent given did not significantly influence the occurrence of nausea and vomiting: among patients treated with daunorubicin, 42% experienced nausea and 34%, vomiting; the respective values for patients treated with mitoxantrone were 32% and 29%. Chlorpromazine rescue was required in 14% of patients receiving daunorubicin and in 13% of subjects receiving mitoxantrone.

Efficacy of high-dose methylprednisolone

Fewer patients in arm B experienced nausea and vomiting (Table 2). This difference reached significance on the 3rd day of treatment and when cumulative 3-day results were considered. Chlorpromazine rescue (total over 3 days) was significantly less frequently necessary in this arm. The severity of symptoms did not appear to differ in the two arms: 64% of symptomatic patients in arm A vs 73% in arm B experienced nausea during >1 h and 44% of vomiting patients in arm A vs 50% in arm B experienced more than two episodes of emesis.

Treatment-related side effects

Neither acute nor chronic dystonic reactions were observed in our patients. The prevalence of severe infectious episodes did not significantly differ in the two arms: nine

documented infections, including three fungal infections were noted in arm A vs five documented infections and no fungal infection in arm B. Overall, five patients in arm A and one in arm B died of either infection or leukemic progression.

Discussion

In this randomized study, we demonstrated that although continuous-infusion metoclopramide and alprazolam appeared to be an effective regimen for the prevention of nausea and emesis as evidenced by the finding that more than two thirds of our patients were asymptomatic on the 1st day of treatment, the addition of high-dose methylprednisolone improved the efficacy of the above-mentioned drugs. In contrast to high-dose metoclopramide (3–7 mg/kg), the intermediate dose used in our study (1.5 mg/kg) does not induce extrapyramidal toxicity [4, 11]. High-dose methylprednisolone might enable the administration of lower doses of metoclopramide. A reduction in anticipatory nausea and vomiting has been found using alprazolam [5]; this activity may explain the improvement noted in the complete control fo nausea and vomiting from day 1 to day 3. Alprazolam administration beginning on the day before the onset of chemotherapy might reduce the proportion of symptomatic patients on the 1st day of treatment.

High-dose methylprednisolone given for 3 days did not increase the incidence of severe infectious episodes in leukemic patients who experienced 15–30 days of chemotherapy-induced aplasia. A better control of nausea and vomiting in leukemic patients might even improve compliance with oral intestinal antimicrobial and antifungal decontamination, therefore reducing the occurrence of severe infectious episodes.

Recently, 5-hydroxytryptamine (serotonin) antagonists have shown impressive activity against cisplatin-induced emesis [6]. However, multiple-day administration of these compounds has not been completely investigated, and if such therapy were efficient, its use might be restricted by its cost. Our data indicate that high-dose methylprednisolone given in association with continuous-infusion metoclopramide and oral alprazolam is a safe and attractive regimen whose cost is moderate.

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