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High-dose Dexamethasone for Prevention of *cis*-Platin-induced Vomiting

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Summary. *Severe, debilitating nausea and vomiting are seen in almost 100% of patients treated with cis-platinum. These side-effects can be so severe and prolonged as to preclude therapy in a large number of patients. Commonly used antiemetics have had only limited success in controlling cis-platinum-induced nausea and vomiting. Various reports have indicated benefits from steroids in this setting.*

We have tested a high-dose dexamethasone regimen with or without neuroleptics, which inhibits chemotherapy-induced vomiting in 50% of patients failing with prior antiemetics and in 71% of those who had not received prior antiemetics. This treatment was administered on an out-patient basis as it involved oral administration of the antiemetic.

Neuroleptic therapy was not randomly assigned, but the results of this pilot study suggest that it did not enhance dexamethasone's efficacy. There were no significant side-effects due to the steroids. The antiemetic effectiveness of dexamethasone was retained through repeated courses of chemotherapy.

Introduction

Nausea, vomiting, and anorexia are common side-effects of therapy with anticancer drugs. These side-effects may be so severe that some patients refuse further treatment even while experiencing an objective tumor regression. For example, an occasional patient with advanced testicular cancer may reject potentially curative therapy [5] with drug combinations containing *cis*-platinum because of the severe vomiting. Of the currently available antineoplastic agents *cis*-platinum is probably the agent with the highest incidence of major nausea and vomiting as a side-effect.

Commonly used antiemetic drugs such as prochlorperazine (Compazine) and thiethylperazine (Torecan) are less than 50% effective in the prevention of vomiting [18]. Several other antiemetics (e.g., diazepam [23, 29], metoclopramide [8, 9, 11, 14, 26], nabilone [13], haloperidol [19, 21, 28], droperidol [10, 17, 30], and delta-9-tetrahydrocannabinol [3, 6, 7, 16, 20, 25]) have shown variable effectiveness. In a pilot study, Baker et al. compared 10 mg dexamethasone IM prior to chemotherapy with placebo. Placebo did not offer any benefit. Fourteen of 20 patients reported marked to moderate relief of nausea and vomiting with dexamethasone. No patient was treated with *cis*platinum [1]. Another clinical study [22] showed that parenterally administered methylprednisolone could almost completely inhibit *cis*platinum-induced nausea and vomiting. On the basis of these reports we initiated a pilot study of high-dose dexamethasone (with or without a neuroleptic) for the control of chemotherapy-related emesis; we placed predominant emphasis on evaluation of this regimen for patients receiving chemotherapy combinations containing *cis*-platinum.

Materials and Methods

Patients receiving chemotherapy at the Cancer Center of the University of Arizona were included in this pilot study.

The results of a small pilot study had shown that a single dose of dexamethasone prior to *cis*-platinum administration was not sufficient to curtail nausea and vomiting. Patients with a history of peptic ulcer disease or diabetes were carefully monitored and advised but not excluded from the trial. The antiemetic regimen was as follows: 8 mg dexamethasone was administered PO the night before treatment, and 4 mg dexamethasone was given every 4–6 h on the day of treatment, supplemented by 10 mg IV (over 5 min) just prior to chemotherapy. The steroid dose was tapered gradually over the next 2 days. Droperidol or haloperidol,

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2–2.5 mg IV, was also administered to 19 of the 34 patients in this trial.

Patients were instructed to fill out a form which evaluated the severity and frequency of emesis and nausea following chemotherapy. They were individually interviewed, the same standard questions being used for each. In addition, their physicians, nurses, and family members were also interviewed, and charts were reviewed to obtain details of their diagnosis and treatment. The following response criteria were used: (1) excellent response – no symptoms or slight nausea; (2) good response – one or two episodes of vomiting and nausea for less than 6 h; (3) poor response – three to five episodes of vomiting over less than 6 h; and (4) no response – nausea for more than 6 h or more than five episodes of vomiting.

Results

Thirty-four patients were studied between September 1980, and February 1981. There were 15 females and 19 males, with a median age of 55 (range 21–83). Twenty-eight patients received *cis*-platinum in doses of 50–75 mg/m^2 every 3–4 weeks or 20 mg/m^2 for 5 days every 3 weeks in various drug combinations, including the following: (1) *cis*-platinum-mitomycin C-vincristine-bleomycin; (2) *cis*-platinum-adriamycin-cyclophosphamide; (3) *cis*-platinum-adriamycin-vinblastine; (4) *cis*-platinum-adriamycin-cyclophosphamide-bleomycin-vincristine-mitomycin C; (5) *cis*-platinum-vinblastine-bleomycin-hexamethylmelamine; and (6) *cis*-platinum-5-fluorouracil-vinblastine-bleomycin. Six patients were treated with non-platinum-containing drug combinations, including actinomycin D, DTIC, hydroxyurea, adriamycin, cyclophosphamide, vincristine, and BCNU. Seven patients had only one treatment and all others had two or more; the mean number of treatments was 2.2.

Table 1 shows the results of antiemetic therapy. Five of ten patients who had previously failed to respond to other antiemetics had an excellent or good response to the dexamethasone regimens. Among 24 patients who received dexamethasone from the beginning of anticancer therapy 62% (neuroleptics added) to 82% (no neuroleptics) had excellent or good antiemetic responses. No alteration of the beneficial antiemetic effects has been observed among patients responding to the dexamethasone regimens, even with up to six courses of therapy. Overall, 22 of the 34 patients (65%) had excellent or good antiemetic responses to dexamethasone alone or with the addition of a neuroleptic. Nineteen of these 22 responders were receiving *cis*-platinum-containing chemotherapy regimens.

The addition of a neuroleptic to dexamethasone did not seem to add to the effect of dexamethasone; however, two patients did have less vomiting when droperidol was added to the steroid regimen.

The antiemetic regimens have been well tolerated. Three patients, whose steroids were discontinued abruptly after 24 h, experienced mild myalgias and malaise and one of them experienced delayed nausea and vomiting. Droperidol therapy was associated with mild to moderate extrapyramidal symptoms in three patients. These side-effects responded promptly to diphenhydramine or biperiden.

Discussion

Severe, debilitating nausea and vomiting are concomitants of chemotherapy with *cis*-platinum-containing drug combinations in almost 100% of

Table 1. Dexamethasone (± neuroleptics) control nausea/vomiting caused by anticancer drug therapy

Prior antiemetic therapy	Neuroleptic Rx (+ or –)	No. of patients and response[a, b]					
		Total	Excellent	Good	Excellent and good	Poor	None
Yes	+	6	2 (2, 6)	1[c] (1)	50%	1 (3)	2 (2, 2)
	–	4	1 (2)	1 (2)	50%	1 (2) + 1[c] (2)	0
	Subtotal	10	3	2	50%	3	2
No	+	13	3 (1, 2, 2) + 2[c] (2, 2)	3 (2, 2, 2)	62%	1 (2)	2 (1, 2) + 2[c] (1, 2)
	–	11	8 (1, 1, 2, 2, 2, 3, 3, 4)	1 (6)	82%	1 (1)	1 (2)
	Subtotal	24	13	4	71%	2	5
All patients		34	16	6	65%	5	7

[a] Response criteria: Excellent, no symptoms or slight nausea; good, one or two episodes of vomiting and nausea for less than 6 h; poor, three to five episodes of vomiting and nausea for less than 6 h; no response, more than five episodes of vomiting or nausea for more than 6 h

[b] ( ) = Number of courses

[c] Rx did not include *cis*-platinum

patients. These side-effects can be so severe and prolonged as to preclude further therapy in a large number of patients. Commonly used antiemetics, such as the phenothiazines (e.g., prochlorperazine) [18] and the neuroleptics (e.g., droperidol and haloperidol) [10, 19, 30], have had only limited success in controlling *cis*-platinum-induced nausea and vomiting. High-dose metoclopramide shows some promise, but has been used with success only IV and is accompanied by some sedation [8, 9, 26]. Using parenterally administered methylprednisolone, Lee et al. [15] have recently reported a 75% reduction of nausea and vomiting (e.g., two or less episodes over 24 hours) in 45 of 55 patients (82%) who were treated with various combination chemotherapies. However, only one of these patients was receiving *cis*-platinum at the time of the steroid therapy. A pilot study of patients receiving *cis*-platinum-based therapy has recently shown a marked benefit of the addition of dexamethasone, 8 mg IV every 3 h for five doses, starting 3 h prior to treatment, to hydroxyzine and prochlorperazine [4].

Based on reports on the antiemetic property of dexamethasone [1] and methylprednisolone [22] we have tested a high-dose dexamethasone regimen (with or without neuroleptic) which can almost completely prevent *cis*-platinum and combination chemotherapy-induced vomiting in 50% of patients who had failed with prior antiemetic therapy and 71% of those who had not received prior antiemtics. This antiemetic regimen was developed to facilitate out-patient anticancer treatment, in that it involves oral administration of the steroids except for the dose immediately prior to chemotherapy. Although this therapy was tested mainly in patients at the initiation of their anticancer drug therapy, it is remarkable that dexamethasone treatment was able to afford excellent or good control of nausea and vomiting in 50% of patients who had failed to respond to standard antiemetics. Furthermore, there was evidence in this trial that the steroid regimen retained its antiemetic effectiveness through repeated courses of chemotherapy.

The results of this pilot study suggest that the addition of a neuroleptic did not usually enhance dexamethasone's antiemetic efficacy. Since the neuroleptic therapy was not randomly assigned, a final decision concerning the combination's efficacy awaits a controlled trial. Further studies of dexamethasone-neuroleptic combinations are needed, since droperidol or haloperidol was only administered once during each course in those patients receiving the combination. In future studies haloperidol could be given orally every 4–6 h along with the repeated dexamethasone dosing. To more fully assess the impact of the addition of dexamethasone on the therapy of cancer patients it will be important to evaluate its effects in a randomized prospective trial comparing it with a non-steroid-containing antiemetic regimen.

The relative lack of side-effects associated with the 60–72 h dexamethasone dosing schedule may recommend it for use instead of the more toxic cannabinoid regimens [3, 6, 7, 13, 16, 20, 25]. As many as 39% of patients treated for their nausea and vomiting with delta-9-tetrahydrocannabinol experienced severe or dose-limiting side-effects [7]. This cannabinoid was especially ineffective in older patients [7], whereas there did not seem to be any impact of age in this oral dexamethasone study. Finally, in two studies delta-9-tetrahydrocannabinol has shown attenuation of antiemetic effects with repeated chemotherapy courses [3, 25].

There is no definite understanding of the antiemetic mechanism of action of the steroids. The antiprostaglandin activity of these drugs could underlie their antiemetic effects. Ibuprofen, a non-steroidal antiprostaglandin agent, also has been shown to control nausea and vomiting induced by radiotherapy [27]. An investigation of this type of agent is warranted. Some controversy has been raised about the risks of steroids in the treatment of cancer patients [12]. Steroids are part of the treatment of most hematologic malignancies and are also widely used in breast cancer. High-dose steroids and other methods of immunosuppression have been shown to increase the number but not the incidence of pulmonary metastases in animals. The survival of steroid-treated animals is significantly better than that of controls [2]. Steroids have been discussed as being inhibitors of the antitumoral effect of *cis*-platinum [24]. We have data from our own laboratory where in vivo, in mice with P388 leukemia, and in vitro, in human cancer cell lines, the addition of steroids to *cis*-platinum did not decrease its effectiveness as an antitumoral agent.

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