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# Does increasing the steroid dose enhance the efficacy of the antiemetic combination of granisetron and methylprednisolone in gynecologic cancer patients—a randomized study

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**Abstract**

*Objective*: The authors administered two doses of oral methylprednisolone in combination with 3 mg granisetron intravenously for the prophylaxis of cisplatin-induced emesis in gynecologic cancer patients. *Materials and methods*: Thirty-nine patients received 100 mg (group A) and 25 received 200 mg (group B) methylprednisolone in the antiemetic combination in a randomized prospective trial. *Results*: No vomiting in 90.2 and 96.7%, one emetic episode in 3 and 1.1% and two episodes in 3 and 2.2% were detected in groups A and B, respectively. More than two emetic episodes were considered to be a failure and were observed only in group A (3.8%). There was no significant difference between the two treatment groups ($P = 0.3160$). *Conclusions*: There was no evidence for enhanced antiemetic effect of elevated steroidal dose in combination with granisetron.


*Keywords:* Granisetron; Methylprednisolone; Antiemesis; Cisplatin-induced emesis

## 1. Introduction

The serotonin (5-hydroxytriptamin) receptor antagonists (setrons) have been widely used for the prophylaxis of the chemotherapy induced emesis/nausea since the 1980s. Despite their beneficial effect, there does remain a group of patients who need some additional antiemesis. Several combinations of antiemetic drugs have been tested to enhance the efficacy. The setron–steroid combinations were found to be the most potent treatments [1–3]. However, the results of the antiemetic therapy with different setrons in adequate doses seem to be equal, therefore several trials were attempted to improve the effectivity by enhancing the steroidal dose of the combinations. In an earlier study, we evaluated the combination of 3 mg intravenous granisetron (GRAN) with 100 mg oral methylprednisolone (MP) in cisplatin-induced acute emesis (CIAE) and found 80.3% complete response (CR) [4]. Looking for a better result, we compared the combinations of 3 mg intravenous GRAN with oral MP of 100 mg (group A) and 200 mg (group B) in gynecologic cancer patients who were receiving cisplatin chemotherapy at a dose of 50 mg/m$^2$ at least. Our clinical observations are described in this paper.

## 2. Material and methods

Sixty-four gynecologic cancer patients were treated with chemotherapy in the Gynecologic Department at the National Institute of Oncology, Hungary in the period of December 2000 and December 2002. Most patients (56 patients) were treated for recurrent ovarian cancer and a smaller group (8 patients) for endometrial cancer. All the patients were given cisplatin-containing chemotherapy with a minimum dose of 50 mg/m$^2$. The doses of cyclophosphamide–epirubicin–cisplatin (CEP) therapy were 500, 60 and 50 mg/m$^2$, respectively, and the doses of cyclophosphamide–cisplatin (CP) treatment were 750 and 75 mg/m$^2$, respectively.

Patients were randomized into two groups according to the two types of antiemetic therapy. All the patients were given 3 mg intravenous GRAN 30 min before chemotherapy. Patients in the groups A and B were receiving 100 and 200 mg oral MP, respectively. Realizing that steroids are contraindicated in some heavy illnesses (i.e. diabetes mellitus), we decided to exclude such diseases. However, we did

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not find such patients in any of the groups, so all patients were given the original steroidal doses.

Thirty-nine patients of the group A got the antiemetic treatment in 132 courses. The minimum number of courses delivered was 1 and maximum 11. Patients' age was 63.2 ± 11 years (range 39–81 years), on average. Twenty-five patients were randomized to group B, their mean age was 59.1 ± 9 years (range 37–75 years). They received chemotherapy in 91 courses (range in a patient 1–7 courses).

Emetic events and all the drugs—including granisetron—used for the antiemetic prophylaxis of chemotherapy in the first 24 h were documented in the protocol of the department. The antiemetic efficacy was evaluated by the scale of the Italian Group of Antiemetic Research [5]. Complete response was defined as the absence of vomiting episodes, major response (MR) as one or two episodes, and failure (F) of the treatment as more than two episodes. Nausea was not evaluated as it is a rather subjective feeling and therefore difficult to monitor exactly.

The GraphPad PRISM (version 2.0) of GraphPad Software Inc. (San Diego, USA) was used for the statistical evaluations. The software PRISM performed the chi-square test for calculations and the difference was defined to be significant in case of $P < 0.05$.

## 3. Results

Thirty-nine patients in group A were treated for recurrent ovarian (36 patients) and endometrial (3 patients) cancer by chemotherapy (CEP: 37 patients; CP: 2 patients). Histology showed serous cystadenocarcinoma in 37 patients and mucinous cystadenocarcinoma in 2 patients. No emesis was noticed in 119 courses (90.2%), one and two emetic episodes were observed in four and four courses (3 and 3%), respectively. The patients developed three emetic episodes in two courses (1.5%) and five times in three courses (2.3%). The results are summarized in Table 1.

The patients in group B were given chemotherapy for recurrent ovarian (20 patients) and endometrial (5 patients) cancer. All the patients had papillary adenocarcinoma but the one clear cell carcinoma. CEP therapy was given in 21 patients and CP therapy was received by 4 patients. In most courses (88), emesis did not developed in the first 24 h after chemotherapy (96.7%). One emetic episode was observed in one course (1.1%) and two episodes in two courses (2.2%).

Table 1
Antiemetic effectivity of 3 mg granisetron treatment in a combination with 100 or 200 mg methylprednisolone

| | No. of patients | No. of courses | CR (%) | MR (%) | F (%) |
|---|---|---|---|---|---|
| Group A | 39 | 132 | 90.2 | 6 | 3.8 |
| Group B | 25 | 91 | 96.7 | 3.3 | – |

CR: complete response; MR: major response; F: failure.

The results were compared by computer (GraphPad software) and no significant difference ($P = 0.7734$; 95% confidence interval: −46.80 to 61.13) was shown between the two antiemetic treatments. We have not found substantial side effects in the two treatment arms either.

## 4. Discussion

The setrons are antiemetic drugs with both peripheral and central effectivity. They can well prevent unpleasant side effects of chemotherapy like emesis and nausea common with many patients. Several drugs have been developed since the 1980s, however, only three of them (granisetron, ondansetron (OND) and tropisetron) spreaded in Europe. Though a fourth drug (dolasetron) with proven value is also available, it is used mostly in America. In clinical studies, the different drugs proved to have nearly identical effectiveness provided that they were administered in prescribed dose [1]. The emetic or retching rate depends on the type and dose of the drug as well as on their combinations with other medicines.

The studies on acute antiemetic effectivity of single setrons showed 44–92% CR [6,7]. As these single drugs did not result in a total CR, several trials were initiated to enhancing the effectiveness. The best results were realized by the combinations with setrons and steroidal drugs. The randomized trials justified the advantage of these combinations over single setrons [3,5,8–10].

The majority of the authors referred to the results of combination treatments with dexamethasone (DEX). DEX was usually applied intravenously in 8 or 20 mg doses (Table 2). A 85–93% CR was reported with the combination of GRAN and 8 mg DEX [10,11] and a 80–94% CR with

Table 2
Antiemetic effectivity of combinations with granisetron and different steroids or steroidal doses

| No. of patients | Granisetron (mg) | Steroid (mg) | CR (%) | Reference |
|---|---|---|---|---|
| 141 | 3 (i.v.) | DEX (8, i.v.) | 85 | [10] |
| 64 | 3 (i.v.) | DEX (12, i.v.) | 95 | [11] |
| 89 | 3 (i.v.) | DEX (20, i.v.) | 81 | [2] |
| 483 | 3 (i.v.) | DEX (20, i.v.) | 80 | [13] |
| 110 | 3 (i.v.) | DEX (20, i.v.) | 81 | [3] |
| 198 | 3 (i.v.) | DEX (20, i.v.) | 94 | [12] |
| 90 | 3 (i.v.) | P (50, p.o.) | 79 | [8] |
| 39 | 3 (i.v.) | MP (10 mg/kg, i.v.) | 85 | [14] |
| 308 | 3 (i.v.) | MP (2× 250, i.v.) | 80 | [9] |
| 31 | 3 (i.v.) | MP (100, p.o.) | 80 | [4] |
| 13 | 3 (i.v.) | MP (125, i.v.) | 92 | [15] |
| 25 | 3 (i.v.) | P (25, p.o.) | 89 | [16] |
| 39 | 3 (i.v.) | MP (100, p.o.) | 90 | Present study |
| 25 | 3 (i.v.) | MP (200, p.o.) | 97 | Present study |

DEX: dexamethasone; MP: methylprednisolone; P: prednisolone; i.v.: intravenous; p.o.: per os.

GRAN and DEX of 20 mg [2,3,12,13]. Other GRAN trials used prednisolone or methylprednisolone as a steroidal compound. Handberg et al. [8] and Sigsgaard et al. [16] evaluated the antiemetic efficacy of granisetron with 50 mg oral prednisolone and found a 79–89% CR. Other authors used methylprednisolone as a steroid in the combination. Hirota et al. found a 85% CR with the 10 mg/kg MP dose [14]. This dose equaled to a 60 mg average MP dose for a woman with a 60 kg average body weight. The steroidal dose was elevated in the studies of Kleisbauer et al. [9], Lehoczky et al. [4] and Ono et al. [15]. They found a 80–92% CR with the use of 2× 250, 100 and 125 mg MP, respectively.

Similar results were shown in the antiemetic combinations of other setrons and steroids. The combination of ondansetron with DEX 20 mg reached a 71–83% CR [2,13,17]. Tropisetron, an other member of this drug family, was also tested in combination with DEX 20 mg, and was found to yield a 64–75% CR [2,18,19].

Despite the above mentioned studies—when setrons and steroids were given in fixed doses—publications are rather sparse on antiemetic combinations with steroid components of randomly rising doses. Münstedt et al. evaluated the antiemetic effectivity of the combination of 5 mg intravenous TROP and 8 or 20 mg intravenous DEX in a randomized study of 69 patients in 1999. Elevation of the steroidal dose did not raise efficacy (64 and 66% CR) [19].

Contributors of the Italian Antiemetic Research Group published a double-blind, dose-finding study on four intravenous doses of dexamethasone in the prevention of cisplatin-induced acute emesis in 1998. The authors summarized all the reports concerning the steroidal dose elevations for a better antiemesis till that time. They found only six reports on combinations with setrons and different steroidal doses in the previous literature. The members of the Research Group evaluated the effectivity of four different doses of DEX in combination with 8 mg intravenous ondansetron in a large double-blind, randomized study [20]. As the former publications were either short reports or abstracts and the optimal dose remained unknown, Italian authors wanted to determine the optimum dose of DEX in the combination with OND for CIAE. The patients were given 8 mg intravenous OND together with 4, 8, 12 or 20 mg intravenous DEX, respectively. The groups included of 133, 136, 130 and 131 patients and the corresponding CR were: 69.2, 69.1, 78.5 and 83.2%, respectively, in the first 24 h after starting cisplatin chemotherapy. A significantly better result (CR) was detected in patients who were given 20 mg DEX instead of those receiving 4 or 8 mg DEX ($P < 0.005$). Patients of the 20 mg DEX group developed a similarly better antiemetic effectivity than those of the 12 mg DEX group, although this difference was not significant. The occurrence of nausea was also less frequent in the 20 mg DEX group than in the other groups, however, the difference between them was likewise not significant [20].

As only few studies are published on dose elevations of steroids in combination with granisetron or other setrons, we evaluated two doses of methylprednisolone (100 and 200 mg) in the combination of 3 mg intravenous granisetron for the prophylaxis of CIAE. We found a better antiemetic effectivity in the combination of the higher steroidal dose. The patients of the groups A and B resulted in a 90 and 97% CR, however, no significant difference was shown between the two antiemetic treatments.

The results confirmed that oral 100 mg MP is sufficient in the antiemetic combination with granisetron. It appears that any further rise in the steroidal dose does not yield higher antiemetic activity. Other clinical studies using various combinations of setrons and anxiolytic drugs are also known, however, they failed to cause a significant change in the elimination of CIAE. A more effective therapy could only be achieved by using less emetic new chemotherapeutic agents/combinations or by new type antiemetics with different mechanisms of action.

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