

# A Randomized Comparison of Granisetron Plus Dexamethason with Granisetron alone for the Control of Acute Chemotherapy-Induced Emesis and Nausea

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## Abstract

**Introduction:** Chemotherapeutic drugs used to treat cancer may cause nausea and emesis by inducing the release of 5-hydroxytryptamine (5-HT) in the small intestine. Blockage of 5-HT<sub>3</sub> receptors in the small intestine by 5-HT<sub>3</sub> receptor antagonists might prevent the nausea and vomiting associated with chemotherapy for cancer. The aim of this study was to compare the efficacy and tolerability of the 5-HT<sub>3</sub> receptor antagonists (granisetron) and granisetron plus dexamethasone in the treatment of acute chemotherapy induced digestive emesis and nausea.

**Materials and Methods:** Patients on their first course of emetic chemotherapy (cisplatin or doxorubicin based regimen) were randomly placed into two treatment groups. Group A received a one-time administration of granisetron 3 mg, IV and group B received granisetron plus dexamethasone 8 mg IV. For each study the drug were administered one time, 30 minutes before infusion of chemotherapy emetic agent. For the efficacy assessment, response data were recorded every 6 hours for a total of 24 hours, after the start of the chemotherapy infusion.

**Results:** A total of 138 patients [86 males, 52 females with a mean age of 48 (a range between 15-82 years)] were involved in the study. Of these, 125 were evaluable.

**Discussion:** The ability of granisetron plus dexamethasone to prevent acute emesis was significantly better than, administering granisetron alone (66.7% vs 42.8% respectively) (p<0.001).

The combination of granisetron and low-dose dexamethasone is superior to granisetron alone to control acute emetic episodes in patients receiving emetogenic chemotherapy.

**Key words:** Nausea, Vomiting, Chemotherapy, Granisetron, Dexamethasone

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## Introduction

The control of chemotherapy-induced emesis and nausea remains an important issue in cancer therapy. The discovery of 5-hydroxy tryptamine 3 (5-HT<sub>3</sub>) receptors in afferent vagal nerve fibers and neurons in the gastrointestinal tract suggests that chemotherapeutic agents such as cisplatin may induce the release of 5-HT<sub>3</sub> in the small intestine, thereby initiating nausea and vomiting by stimulating the vagus nerve.(1,2) Research shows that chemotherapy agents such as cisplatin cause nausea and vomiting in more than 70% of patients.(3)

Therefore, blockage of the 5-HT<sub>3</sub> receptors in the small intestine by a 5-HT<sub>3</sub> receptor antagonist (RA<sub>5</sub>) might prevent the initiation of this reflex.

Granisetron, another serotonin-receptor antagonist, is also effective in controlling acute emesis with more prolonged activity.(4,5)

Furthermore, larger multicenter randomized trials have shown that a combination of a 5-HT<sub>3</sub> receptor antagonist with a corticosteroid is significantly more effective than a 5-HT<sub>3</sub> antagonist alone. In these trials, the combination of a 5-HT<sub>3</sub> receptor antagonist with a corticosteroids has been shown to yield an approximately 75% (range 58-96%) complete control rate of acute emesis after a high dose, cisplatin- based regimen.(6,7)

To evaluate the role of a 5-HT<sub>3</sub> antagonist, in particular, granisetron plus corticosteroids (specifically dexamethasone) in the prevention of acute emesis, we organized a single-institution, randomized prospective, open study comparing granisetron plus dexamethasone, with granisetron alone in chemotherapy treated patients.

## Materials & Methods

We conducted a prospective comparative clinical trial study during 2003-2004. The sample number of patients enrolled in the study was 138. One hundred twenty-five patients were evaluated for efficacy according to the intention-to-treat principle. Thirteen patients were lost to follow-up and excluded from the analysis of the assessable and eligible patients. Sixty-three patients received granisetron alone (group A) and 62 patients received granisetron plus dexamethasone (group B) as a maintenance treatment.

Male and female cancer patients aged 15-82 years were eligible to participate in this study if they had been scheduled to receive their first course of chemotherapy (30-80 mg/m<sup>2</sup> cisplatin or >40mg/m<sup>2</sup> doxorubicin) administered as a single IV infusion over a period of up to 4 hours. Each drug was used alone or in combination with other cytotoxic drugs.

Patients were excluded from the study if they had received radiotherapy or if they had gastrointestinal obstruction, severe cardiac disease, renal disease, hepatic disease, vomiting induced by intracranial metastases, or intracranial hypertension, currently using corticosteroids, recent changes in the doses of major tranquilizers or habitually using sleeping pills or had evidence of severe uncontrollable diabetes. Written, informed consent was obtained from all patients and the participating physicians informed the patients of the details of the study.

**Study design:** We conducted a single-blind prospective-clinical trial comparative study. The blind group in this study were all patients participating in the study. Sampling was accessible (convenience). Sample size was 138 patients (based on,  $n=2(Z\alpha+Z\beta)^2 P(1-P)$ ,  $P= 0.7$ ,  $Z\alpha= 1/96$ ,  $Z\beta= 0.84$ ,  $d= 0.2$ ).

One hundred thirty-eight patients were enrolled in the study and 125 patients were evaluated for efficacy according to the intention-to-treat principle. Thirteen patients were lost to follow-up and excluded from the analysis of the assessable and eligible patients.

Sixty-three patients were randomly selected to participate in group A and 62 patients in group B.

Patients were randomly assigned to receive either granisetron alone (group A) and granisetron plus dexamethasone (group B). Patients were selected one by one in groups A and B based on a systematic random allocation.

One group received a single IV dose of granisetron 3 mg and the other group received granisetron 3 mg IV plus dexamethasone 8 mg IV, 30 minutes before the infusion of chemotherapy.

Patients were assessed for 24 hours after the start of the chemotherapy infusion. The timing and number of emetic episodes were recorded for the purpose of this study. The response criteria for emesis were as follows: completely effective (0 emetic episodes), moderately effective (1-2 emetic episodes), slightly effective (3-5 emetic episodes) and not effective ( $\geq 6$  emetic episodes).

The response criteria for nausea were as follows:

Moderately effective (did not interfere with normal daily life), slightly effective (interfered with normal daily life) or not effective (patients were bedridden due to nausea).

The severity of these events and their relationship to the treatment study were assessed by the evaluator.

The Fisher exact test was used to examine the differences in efficacy and the incidence of adverse events. Statistical significance was set at  $p<0.05$ . Mann-whitney u-test was performed to compare treatment groups with respect to the intensity of nausea and the number of emetic episodes.

## Results

A total of 138 patients were enrolled into the study. One hundred five patients were evaluated for efficacy according to the intention-to-treat principle.

Thirteen patients were lost to follow-up and excluded from the analysis of the assessable and eligible patients, 63 patients received granisetron alone (group A) and 62 patients received granisetron plus dexamethasone (group B) as a maintenance treatment.

The treatment groups were analyzed according to sex and age groups as well as the cisplatin dosage amount (table 1)

A completely effective response (0 emetic episodes) was achieved by (n=42), 66.7% granisetron plus dexamethasone for the treatment of patients and 42.8% (n=27) in patients treated with granisetron during 24 hour period after the administration of chemotherapy. This difference was statistically significant ( $p<0.001$ ) (table 2).

Twenty-six granisetron treated patients (41.3%) and 35 granisetron plus dexamethasone treated patients

(56.4%) did not experience nausea during the 24 hours after chemotherapy.

**Table1 : Demographic and disease characteristics of the study patients**

	Granisetron	Granisetron plus Dexamethasone
<b>Number of patients</b>	63	62
<b>Male/Female</b>	21/42	25/37
<b>Median age (range)</b>	64 (40-72)	63 (20-70)
<b>Cisplatin dose (mg/m<sup>2</sup>):</b>		
<60	13	14
>60	50	48
<b>Primary tumors:</b>		
GIT	20	20
Breast	22	21
Hematology	21	21

**Table-2. Comparison between the effects of two regimens on chemotherapy induced emesis.**

	Group A N=63	Group B N=62	p-value
<b>Complete effect</b>	42.8%	66.7%	<0.001
<b>Moderately*</b>	30.2%	27%	<0.08
<b>Slightly</b>	23.8%	6.3%	<0.03
<b>Not effective</b>	3.2%	0%	<0.02

\*p<0.05 is significant compared two group.

This difference was statistically significant in combination therapy compared with the treated patients who were given granisetron alone.

The incidence of adverse events did not differ significantly between the two groups. No severe or unexpected drug-related adverse events were observed after either treatment. The most common adverse event in the granisetron group A (n=63) were headache 9 (14.2%) dry mouth 10 (15.8%) and tiredness 15 (23.8%).

The most common adverse event in group B (n=62) were tiredness 14 (22.5%) and headache 8 (12.9%).

## Discussion

This study showed that a combination of granisetron (3mg IV) plus a low dose dexamethasone (8mg IV) is superior to granisetron alone to control acute emetic episodes in patients receiving emetogenic chemotherapy (p<0.001).

In our study, the complete effect of granisetron in group A was 42/8%, while in group B (receiving granisetron plus dexametasone) was 66/75. In the Smith study in London, the complete effect of anti-serotonin was 30% and in antiserotonin plus dexametasone 78%. The Avarez study in America showed that the complete effect of anti-serotonin was 23% and in anti-serotonin plus dexametasone 61%. The Van belle study showed the complete effect of Novabon (antiserotonin) was 72% and

Novabon plus dexametasone, 76%. Also, the rate of complete protection from acute and delayed vomiting/nausea in the Liaw study were 97/3%/93/2% and 71/2%/60/3%, respectively.

Several randomized trials have shown that the addition of corticosteroids to 5-HT<sub>3</sub> antagonists significantly improved the control of acute emesis.(6,7,8,9,14,15,16,17)

Although a review of other results of our study showed that anti-serotonin plus dexamethasone is superior to granisetron (or antiserotonin) alone in the control of acute emetic episodes in patients receiving cisplatin, there are differences between the rates of recovery with the use of dexamethasone. Perhaps a reason for this is the methods applied in our study and other studies because we used a low dose dexamethasone (8mg, IV, one dose). In other studies such as Smith, Van belle, Alvarez and Liaw, the high dosage of dexamethasone was used (8mg, 2-3 days in six-nine doses or 20mg dexamethasone in Liaw study).(8,9,16,17)

Another study showed that a single-dose of dexamethasone IV at a dosage of 20 mg is a safe and effective anti-emetic for patients receiving cancer chemotherapy, excluding cisplatin.(10,14)

Aapro, et al studied 131 patients showing a combination of oral dexamethasone and oral granisetron with an extremely effective control of acute emesis (86% protection).(11)

Many patients in the Aapro study had been given moderately emetic chemotherapy and had an excellent rate of acute control with granisetron 2 mg and dexamethasone.(11) However, emerging data indicates that a 1 mg granisetron oral dose may be sufficient for such patients.(12)

The 8 mg dose of dexamethasone used in this study for acute emetic control might be too low for patients receiving cisplatin-based chemotherapy, where 20 mg has been suggested as a standard. (13) However, for the majority of our patients, this combination was excellent with a 66.7% acute control rate.

Based on the findings, dexamethasone plus granisetron cannot be used as a routine drug in preventing nausea & vomiting. It is recommended that the oncologist pay attention to the amount of prescribed doses of dexamethasone used as an antiemetic prophylaxis during chemotherapy containing cisplatin.

In our study, the incidence of a lack of nausea in patients receiving granisteron was 41/3% and 57/2% in patients receiving granisetron plus dexamethasone, while in the Alvarez study, the

incidence of lack of nausea was 52% in patients receiving ondansetron and 74% in patients receiving ondansetron plus dexamethasone.

Perhaps the reason for this difference is that methods and sample sizes applied in our study and the Alvarez study are different. In our study, low dose dexamethasone and but in the Alvarez study, high dose dexamethasone was used on 33 patients. It is recommended that oncologists pay attention to the amount of prescribed doses of dexamethasone.

### Conclusion

In this study, the efficacy and safety of granisetron plus low dose dexamethasone proved better than using granisetron alone in patients given chemotherapeutic agents that often cause nausea and emesis.

At present, the gold standard for acute antiemetic protection against highly or moderately emetogenic chemotherapeutic agents is a combination of a 5-HT<sub>3</sub> antagonist and a corticosteroid.

Dexamethasone is an effective antiemetic with no known interaction with the serotonin antagonist. Dexamethasone should be added, unless a clearly documented reason for not using a corticosteroid in a patient has been demonstrated.

More effective agents for control of emesis can only improve the quality of life in our patients and make chemotherapy more tolerable.

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