Comparison of Gabapentin, Prochlorperazine and Ondansetron for Prevention of Delayed Chemotherapy-Induced Nausea and Vomiting

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Abstract: Background: Patients beginning cancer treatment consistently list chemotherapy- induced nausea and vomiting as one of their greatest fears. Inadequately controlled emesis impairs functional activity and quality of life for patients, increases the use of health care resources and may occasionally compromises adherence to treatment. The goal of this study was to compare the effectiveness of gabapentin, prochlor- perazine and ondansetron in prevention of delayed chemotherapy induced nausea and vomiting in cancer patients receiving highly and moderately emetogenic chemotherapy. **Patients and methods:** 125 chemotherapy-naive cancer patients, who were scheduled to receive moderately and highly emetogenic chemotherapy were enrolled in the study. Patients were stratified according to gender, age and they were allocated to one of three groups: Group I: received 20mg oral dexamethasone with 5HT3 receptor antagonist ondansetron (Zofran®) 24 mg on day1 and oral gabapentin 300mg once daily on day 2 through 6 of chemotherapy. Group п: received 20mg oral dexamethasone with 5HT3 receptor antagonist ondansetron (Zofran®) 24mg on day1, and oral prochlorperazine (Emedrotec®) 3mg twice daily on day 2 through 6 of chemotherapy. Group ш: received 20 mg oral dexamethasone with 5HT3 receptor antagonist ondansetron (Zofran®) 24mg on day1 and oral ondansetron (Zofran®) 8mg daily on day2 through 6. The average severity of nausea and vomiting during days 2 to 6 after chemotherapy was assessed for every patient, using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) and this assessment was repeated for every chemotherapy cycle for 6 cycles. Results: The reported average severity of nausea during cycles 1, 2, 3,6 was lower in patients receiving ondansetron and gabapentin compared to emedrotec (p<0.05). As regard average severity of vomiting scores there was significant decrease in vomiting scores in patients received either gabapentin or ondansetrone in cycles 2,3,4,5,6 compared to patients received emedrotec (p<0.05). A percentage of patients required rescue medication to alleviate CINV during the study period, 8(19.5%) patients taking ondansetrone compared with 10 (24.3%) patients in the gabapentin group and 17(39.5%) patients in the Emedrotec group. Rescue medication used was ondansetron (zofran®) 24 mg IV. Inter groups comparison for the DN4 during the 6 cycles showed significant reduction in the gabapentin group compared to both emedrotec and ondansetrone groups (p<0.05). The incidence of neuropathic pain (DN4 ≥ 4) was significantly reduced in gabapantin group in the 3rd cycle compared to emedrotec and ondansetrone groups (p =0.048). Conclusion: Gabapentin, ondansetron, and prochlorperazine are useful drugs for the management of delayed chemotherapy- induced nausea and vomiting. Ondansetron and gabapentin are more effective than the prochlorperazine. Gabapentin did not only reduce CINV, it also reduced chemotherapy-induced neuropathic pain.

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1. Introduction

Patients beginning cancer treatment consistently list chemotherapy- induced nausea and vomiting as one of their greatest fears [1,2]. Inadequately controlled emesis impairs functional activity and quality of life for patients, increases the use of health care resources and may occasionly compromises adherence to treatment [3,5]. Pioneering studies conducted by **Wang and Borison** nearly 60 years ago proposed the concept of a central site (vomiting center) located in the medulla that serves as a final common pathway for processing all afferent impulses that can initiate emesis [6]. It is now thought that an anatomically discrete vomiting center is unlikly to exist [7].

Rather, a number of loosely organized neuronal areas within the medulla probably interact to coordinate the emetic reflex [8, 9]. The neurons coordinating the complex series of events that occur during emesis have been termed "central pattern generator" [10,11]. CINV is categoraized accoding to timing of its occurance relative to the administration of chemotherapy. Acute CINV describes nausea or vomiting that occurs during the 24 hours following a dose of chemotherapy; it generally reaches a peak of intensity after 5-6 hours [12]. Delayed CINV refers to nausea or vomiting that begins at least 24 hours following the dose of chemotherapy. For example, the intensity of CINV in patients receiving treatment with cisplatin- based chemotherapy (classified as HEC) may be at its heighest 48-72 hours after treatment and can last for up to a week [12]. Breakthrough CINV describes nausea and /or vomiting that occurs despite the use of CINV prophylaxis and requires active management with rescue medication [12]. Early attempts to control chemotherapy- induced nausea and vomiting (CINV)

included corticosteroids and selective 5-hydroxy-tryptamine 3

(5-HT3) receptor antagonists [13,15]. The efficacy of 5-HT receptor antagonists significantly improved when they are combined with corticosteroid [16, 17].

Prochlorperazine is a member of phenothiazine group of neuroepleptic drugs which in doses lower than those used in psychiatry is employed for its anti- emetic properties with its site of action is thought to be the chemoreceptor´s trigger zone. Prochlorperazine was compared with dexamethasone after moderately to highly ematogenic chemotherapy and proved to have equivalent outcome in term of controlling vomiting, measure of satisfaction and quality of life [18].

Gabapentin, a structural analog of gamma aminobytric acid (GABA), is an antiepileptic drug. Recently, an open clinical study demonstrated the anti-emetic effect of gabapentin in chemotherapy- induced acute (within 24hrs) and delayed onest (days 2-5) of nausea and vomiting in breast cancer patients with support from other randomized trials for using this drug in controlling the symptoms of CINV[19]. Gabapentin is a γ-aminobytric acid analogue with an established history in treating epilepsy, chronic neuropatnic pain, postoperative pain and post herpetic neuralgia [20–22].

The Goal of this study was to compare the effectiveness of gabapentin, prochlor- perazine and ondansetron in prevention of delayed chemotherapy induced nausea and vomiting in cancer patients receiving highly and moderatly emetogenic chemotherapy.

2. Methods:

This randomized study was approved by local ethics committee of the South Egypt cancer Institute, Assiut University, Egypt. After written informed consent, 125 chemotherapy-naive cancer patients, scheduled to receive moderately and highly emetogenic chemotherapy were enrolled in the study.

Inclusion criteria

ECOG performance status 0-2, life expectancy ≥ 3 months, serum creatinin ≤ 1.5 times upper limit of normal within the past 30 days, normal liver function ,and blood picture , able to complete questionnaire(s) by his/ herself or with assistance, able to swallow pills.

Exclusion criteria

Pregnancy or lactation, gastrointestinal obstruction, history of nausea or vomiting related to any medical condition or other medications, history of allergy to the study drugs, previous exposure to chemotherapy, prior or concurrent aprepitant or any other NK-1 receptor antagonist, and concurrent pelvic or abdominal radiotherapy.

Patients were stratified according to their gender and age, and they were allocated to one of three groups:

Group I: received 20mg oral dexamethasone with 5HT3 receptor antagonist ondansetron (Zofran®) 24 mg on day1 and oral gabapentin 300 mg once daily on day 2 through 6 of chemotherapy.

Group II: received 20mg oral dexamethasone with 5HT3 receptor antagonist ondansetron (Zofran®) 24mg on day1, and oral prochlorperazine (Emedrotec®) 3mg twice daily on day 2 through 6 of chemotherapy.

Group III: received 20 mg oral dexamethasone with 5HT3 receptor antagonist ondansetron (Zofran®) 24mg on day1 and oral ondansetron (Zofran®) 8mg daily on day 2 through 6.

The average severity of nausea and vomiting during days 2 to 6 after chemotherapy was assessed for every patient, using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (23) and this assessment was repeated for every chemotherapy cycle for 6 cycles. The mean nausea and vomiting score for every cycle was calculated.

National Cancer Institute's Common Terminology Criteria for Adverse Events: N&V[a]

Adverse Event	Grade	Description
Nausea[b]	1	Loss of appetite without alteration in eating habits
	2	Oral intake decreased without significant weight loss, dehydration, or malnutrition
	3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
	4	Grade not available
	5	Grade not available
Vomiting[c]	1	1–2 episodes (separated by 5 min) in 24 hrs
	2	3–5 episodes (separated by 5 min) in 24 hrs
	3	≥6 episodes (separated by 5 min) in 24 hrs; tube feeding, TPN, or hospitalization indicated
	4	Life-threatening consequences; urgent intervention indicated
	5	Death

Evaluation of chemotherapy evoked neuropathic pain by Douleur Neuropathique (DN4) score [24]. DN4

was assesed every cycle for six cycles. Total score equals 10. If the patient score is ≥ 4, neuropathic pain is diagnosed. Adverse effects of the study drugs such as headache, dizziness, cardiac arrhythmia, concitpation, diarrhea and dry mouth were treated and recorded.

Statistical analysis

Analysis was performed using the SPSS soft ware version 17 (Chicago- USA). Data were expressed as mean ± SD, number and frequencies. Parametric data were analyzed using ANOVA test among groups followed by post-hoc test if needed. Kruskal Wallis test was used to compare non-parametric data among groups. Mann-Whitney test was used to compare non parametric data between two groups. The Chi-square test was used to analyze frequency and percentage. A p-value <0.05 was considered statistically significant.

3. Results

A total of 125 patients were enrolled into the study (Table1). 72.8% of the study population were women, and most patients were dignosed with either breast or heamatological malignanacy. The combination chemotherapy regimens included highly emetgenic agents as cisplatin or decarbazine which were given to 32.8% of the included patients. 67.2% of our patients received moderately emotegenic agents as anthracycline, carboplatin or cyclophosphamide based chemotharepy.

The primary aim for this study was to test for differences between the three antiemetics in the average nausea and vomiting score reported on days 2 through 6 for 6 chemotherapy cycles (Table 2).

The reported average severity of nausea during cycles 1, 2, 3, 6 was less in patients receiving ondansetron and gabapentin compared to emedrotec (p<0.05) (Table 2).

As regard average severity of vomiting scores there was significant decrease in vomiting scores in patients recived either gabapentin or ondansetrone in cycles 2,3,4,5,6 compared to patients received emedrotec (p<0.05) (Table2).The number of patients experienced no nausea and no vomiting during the 6 cycles of chemotherapy are showed in table (3).

The percentage of patients required rescue medication to alleviate CINV during the study period was 19.5% (8 patients) in ondanosetrone group compared with 24.3% (10 patients) in the gabapentin group and 39.5% (17 patients) in the emedrotec group. Rescue medication used was ondansetron (zofran®) 24 mg IV.

Inter groups comparison for the DN4 during the 6 cycles showed significant reduction in the gabapentin group compared to both emedrotec and ondansetrone groups (p<0.05). The incidence of neuropathic pain (DN4 ≥ 4) was significantly reduced in gabapentin group in the 3rd cycle compared to emedrotec and ondansetrone groups (p =0.048) (Table 4).

Cardiac arrhythmia was absent in all study groups and there was no significant difference between groups in incidence of headache, dizziness, constipation, diarrhea, and flushing (p>0.05) (Table 5).

Table (1): Demographic data

Gender	Male	34 (27.2%)
	Female	91 (72.8 %)
Cancer type	Head and neck	4 (3.2%)
	Lung caner	4 (3.2 %)
	Breast cancer	51.2%) (64
	GIT	20 (16 %)
	Genitourinary	7 (5.6%)
	Hematological	25 (20%)
	Others	1 (0.8%)
Chemotherapy.	Moderate ematogen	84 (67.2 %)
	Highly ematogen	41 (32.8 %)
Antiemetic drugs	Gabapentin Emedrotec Ondanosetron	41(32.8%) 43(34.4) 41(32.8%)

Data are expressed as number and %

4. Discussion

CINV management has become a fertile area for pharmacological research, resulting in a range of antiemetic interventions undreamt of 20 years ago. And the development of evidence- based treatment strategies supported by international guide lines [12,25,26]. The current study demonstrated that the average severity of nausea during cycles 1,2,3,6 was reported lower in patients receiving ondansetron and gabapentin compared to emedrotec (p< 0.05). Also there was a significant reduction in the severity of vomiting scores in cycles 2,3,4,5,6 in patients received either gabapentin or ondansetron compared to patients received emedrotec (p <0.05). The percentage of patients required rescue medication ondansetron (zofran) 24mg IV to alleviate CINV was (24.3%) in group I:, (39.5%) in group II and was (19.5%)in group III. Most of the patients in our study were females (72.8%), and most patients were diagnosed with either breast or haematological malignancy. The highly emetogenic agents were given to 32.8 % of patients and 67.2% of our patients received moderately emetogenic agents. In agreement with our study **Guttuso *et al.,*** (27) reported an improvement in CINV in six of nine breast cancer patients when gabapentin was used to prevent nausea. **Cruz *et al.,*** (28) added gabapentin to ondansetron, dexamethasone, and ranitidine to prevent CINV in patients receiving HEC (highly emetogenic chemotherapy). The CR (complete response; no emesis, no use of rescue medication) rate

was significantly improved in the patients receiving gabapentin, but nausea was not significantly improved (no nausea, overall period:62% VS 45%;. The role of gabapentin in preventing CINV was less clear. **Guttuso *et al.,*** reported the results of a small open-label study of nine patients with nausea and vomiting after the first cycle of moderately emetogenic chemotherapy. The authors postulated that the mitigation of the takykinin neurotransmitter might play a role in the prevention of CINV. Howerver, the real mechanism of action of gabapentin as an antiemetic agent is not known [27]. Emesis is an autonomic reflex controlled by multiple neurotransmitter systems. Blocking both the 5- HT3 receptor and substance P/NK1 receptors has been demonstrated to reduce CINV in patients receiving chemotherapy. A three drug regimen of 5-HT3 receptor antagonists (ondansetron, granisetron, palonosetron), NK-1antagonists (aprepitant, casopitant) and corticosteroids (dexamethasone) is currently the standared treatment for the prevention of CINV in patients receiving moderately emetogenic chemotherapy [29,30]. In our study when recording side effects of drugs there were no serious side effects in all study groups. Neuropathic pain induced by chemotherapy and evaluated by Douler Neuropathie (DN4) score in all cycles in all groups, was significantly reduced in the gabapentin group compared to the other two groups ($p<0.05$). Gabapentin had a benefit in not only reducing CINV , but also reducing chemotherapy induced neuropathic pain, and this was in agreement with **Tsavaris *et al.*,** [31] who concluded that gabapentin monotherapy seems to be well tolerated and useful for management of chemotherapy – induced neuropathic pain . **Caraceni *et al.,*** [32] administered gabapentin as an "add- on" therapy for at least 1 week to 22 cancer patients with neuropathic pain partially responsive to opiate treatment and found that global pain , burning pain,shooting pain episodes, and allodynia decreased in intensity and frequency . Overall, 20 patients (90%) judged the drug "efficacious" in relieving their symptoms.

Our study showed that Gabapentin, ondansetron, and prochlorperazine are useful drugs for the management of delayed chemotherapy- induced nausea and vomiting. Ondansetron and gabapentin are more effective than the prochlorperazine. Gabapentin not only reduce CINV, it also reduced chemotherapy-induced neuropathic pain.

Table (2): Nausea and vomiting scores (CTCAE)

	Gabapentin (n=41)	Emedrotec (n=43)	Ondansetron (n=41)	*p*-value#
Nausea				
• 1st Cycle	1.51 (1.00)*	1.84 (2.00)	1.44 (1.00)*	0.007
• 2nd Cycle	1.66 (1.00)*	2.16 (2.00)	1.61 (1.00)*	0.002
• 3rd Cycle	1.63 (1.00)*	2.23 (2.00)	1.73 (2.00)*	0.009
• 4th Cycle	1.54 (1.00)	1.91 (2.00)	1.66 (1.00)	0.102
• 5th Cycle	1.73 (1.00)	1.98 (2.00)	1.80 (1.00)	0.162
• 6th Cycle	1.61 (1.00)*	2.02 (2.00)	1.44 (1.00)*	0.007
Vomiting				
• 1st Cycle	1.39 (1.00)	1.74 (1.00)	1.46 (1.00)	0.220
• 2nd Cycle	1.39 (1.00)*	1.81 (1.00)	1.56 (1.00)*	0.049
• 3rd Cycle	1.46 (1.00)*	1.86 (2.00)	1.34 (1.00)*	0.009
• 4th Cycle	1.39 (1.00)*	1.91 (1.00)	1.56 (1.00)*	0.049
• 5th Cycle	1.37 (1.00)*	1.98 (2.00)	1.39 (1.00)*	0.005
• 6th Cycle	1.29 (1.00)*	2.07 (2.00)	1.59 (1.00)*	0.002

Data was presented as mean (median) score
p was calculated using Kruskal Wallis H test
*= Significant to control group

Table (3): Number of patients experienced no nausea and no vomiting

	Gabapentin (n=41)	Emedrotec (n=43)	Ondansetron (n=41)
No nausea			
• 1st Cycle	12	1	2
• 2nd Cycle	10	1	2
• 3rd Cycle	13	2	17
• 4th Cycle	10	3	14
• 5th Cycle	14	3	12
• 6th Cycle	9	2	7
No vomiting			
• 1st Cycle	13	20	24
• 2nd Cycle	14	4	20
• 3rd Cycle	18	10	20
• 4th Cycle	15	5	18
• 5th Cycle	16	2	15
• 6th Cycle	13	5	14

Data are expressed as numbers

Table (4): The Douleur Neuropathique (DN4) score.

Score	Gababentin (G1)	Emedrotec (G2)	Ondansetron (G3)	*P*-value
DN4 (1st cycle)				
Total score	1.78±0.14	1.80±0.14	1.65±0.13	0.711
≥4	1(2.43%)	4(9.30%)	3(7.31%)	0.395
DN4 (2nd cycle)				
Total score	0.78±0.15*	3.08±1.39	2.72±0.23	0.001
≥4	3(7.31%)	9(20.93%)	7(17.07%)	0.177
DN4 (3rd cycle)				
Total score	1.22±0.14*	2.82±0.17	2.42±0.20	0.001
≥4	2(4.87%)*	9(20.93%)	8(19.5%)	0.048
DN4 (4th cycle)				
Total score	1.58±0.16*	2.85±0.18	2.56±0.23	0.001
≥4	3(7.31%)	10(23.25%)	9(21.95%)	0.092
DN4(5th cycle)				
Total score	1.72±0.18*	3.08±0.17	2.67±0.24	0.001
≥4	5(12.19%)	14(32.55%)	12(29.26%)	0.054
DN4 (6th cycle)				
Total score	1.92±0.20*	3.35±0.21	2.69±0.21	0.001
≥4	4(9.75%)	12(27.9%)	10(24.39%)	0.052

Data are expressed as mean ± SD, numbar (%)
*= significant to control group

Table (5): Side effects

Score	Gababentin (G1)	Emedrotec (G2)	Ondanosterone (G3)	*P*-value
1-Headache	5 (12.1%)	3 (6.97%)	6 (14.63%)	**0.574**
2-Dizziness	4 (9.75%)	1(2.3%)	2 (4.87%)	**0.352**
3-Cardiac arrhythmia	0(0%)	0(0%)	0(0%)	**------**
4-Concitpation	(14.63%) 6	7 (16.27%)	5 (12.1%)	**0.826**
5-Diarrhea	8 (19.51%)	9 (20.93%)	7(17.07%)	**0.859**
6-Dry mouth	1(2.4%)	4(9.30%)	0 (0%)	**0.047**

Data are expressed as number (%) and *p*- value

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