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REDUCING THE COSTS OF CHEMOTHERAPY ANTIEMETIC PROPHYLAXIS: RESULTS OF A PILOT SINGLE INSTITUTION RANDOMIZED DOUBLE BLIND TRIAL COMPARING STANDARD DOSE ONDANSETRON VERSUS LOW DOSE GRANISETRON

Redução dos custos da profilaxia antiemética: resultados de um estudo piloto uniinstitucional duplo-cego e randomizado comparando uma dose padrão de ondansetron com granisetron em baixa dose

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The serotonin receptor antagonists such as Granisetron (GRA) and Ondansetron (OND) are effective but expensive antiemetic medications. In this study, we compared the antiemetic efficacy of a cheaper intravenous (IV) regimen of the lowest recommended dose of GRA (10 μg/kg), with that of a standard 32 mg IV dose of OND given before moderately or highly emetogenic chemotherapy in previously untreated cancer patients. Eighty patients were randomized, 45 to GRA and 35 to OND. Both groups were comparable regarding age, sex, alcohol consumption and emetogenic potency of the chemotherapy regimens received. The efficacy of these drugs was measured 24h after their administration. Complete protection from vomiting, nausea, and both nausea and vomiting occurred in 68,5 versus 46.6% (p = 0.083), 45% versus 40% (p = 0.77) and 42% versus 22 % (p = 0.08) of the patients treated with OND and GRA, respectively. There were no statistical differences between groups regarding the number of emetic episodes, nausea intensity or quality of life (QOL) scores measured through the Functional Living Index of Emesis (FLIE) questionnaire. The acquisition costs of the GRA regimen was about 5 times lower than that of the OND regimen. We conclude that despite of a trend favoring OND over GRA in terms of antiemetic efficacy, QOL scores were similar. Therefore, because of the large difference in the acquisition costs of these two regimens, GRA at the dose of 10 μg/kg IV seems to be an acceptable alternative to the more expensive regimen of 32 mg IV of OND.

Unitermos:
Keywords: *Granisetron. Ondansetron. Antiemetics. Serotonin antagonists.*

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Introduction

The high efficacy in the prevention of chemotherapy induced nausea and vomiting (CHTEM) afforded by the new serotonin antagonists decreased substantially the incidence of these unpleasant chemotherapy side effects[1]. Unfortunately, however, the high costs of these medications limit their widespread use, specially for underserved populations living in developing countries.

Several studies have already compared different serotonin antagonists for the prophylaxis of CHTEM. It was not clear, however, in the several randomized comparative studies[2,10] done so far that any of these medications is superior in terms of antiemetic efficacy. Therefore, issues relating to costs and patient's quality of life (QOL) assume an important role in the choice of any of these drugs for institutional antiemetic protocols.

Aiming at decreasing the costs involved in the CHTEM prophylaxis, we undertook randomized, double blind trial in

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Acta Oncol. Bras. Vol. 20 - nº 03, 121-126, jul-ago-set, 2000

our own institution to compare the antiemetic efficacy, toxicity as well as the impact on the QOL scores of the lowest effective dose of GRA described in the literature (ie 10 μg/kg)[5,11] with a standard 32 mg IV dose of OND[12].

Patients and methods

83 patients treated with chemotherapy according to our Institutional protocols at the outpatient oncology unit of the ABC Foundation School of Medicine from April 1997 through June 1999 were enrolled in this study, after signing the informed consent form approved by our IRB. Initially we enrolled only patients that would be receiving highly emetogenic chemotherapy. After the study was open for accrual, we decided to include also patients who were to receive moderately emetogenic chemotherapy as well.

Patients were included if they were older than 18 and were scheduled to receive moderately or highly emetogenic chemotherapy. We defined as moderately or highly emetogenic chemotherapy regimens that contained either Doxorubicin at a dose higher or equal to 50 mg/m^2 or Cisplatin at a dose higher or equal to 60 mg/m^2, respectively.

We excluded patients: a) previously treated with chemotherapy; b) with other potential causes of vomiting such as cerebral metastasis, gastrointestinal obstruction, or radiation therapy to the abdomen; c) with any nausea or vomiting in the 24 hours prior to study entry; d) taking other medications with potential antiemetic activity such as corticosteroids and neuroleptics. Pregnant patients were also not allowed to participate in this study. Three of the 83 enrolled patients were excluded, two because of corticosteroid administration and one lost of follow up.

Patients were randomized to treatment with Granisetron (GRA) 10 μg/kg or Ondansetron (OND) 32 mg both given intravenously 30 minutes before chemotherapy on a double-blinded fashion. We stratified patients according to emetogenic potential of the chemotherapy (highly versus moderately emetogenic) and within the highly emetogenic group, according to sex. Since the moderately emetogenic group consisted only of women receiving Doxorubicin-based chemotherapy regimens for breast cancer, no sex stratification was necessary within this subgroup.

We defined vomiting as the elimination of gastric contents through the mouth and considered as two episodes if they occurred at least one minute apart. We defined nausea as the sensation of imminent vomiting and we graded from it on a scale of severity ranging from 1 (very mild) to 5 (severe). For patients with more than one episode of nausea, we reported only the most severe one. Complete control of vomiting (CCV), nausea (CCN) and of both nausea and vomiting (CCNV) were defined as absence of any episode of vomiting, nausea and both (nausea and vomiting), respectively. We also recorded the time in hours of the first emetogenic episode (nausea and/or vomiting) Patients received non-serotonin antagonists rescue antiemetics such as dimenidrate or metoclopramide to be used at home, as needed, after chemotherapy.

After initial evaluation, eligible patients signed informed consent forms. Patients were then evaluated 24 hours after chemotherapy administration when they brought a diary reporting any emetogenic episodes experienced. They were also interviewed for data accuracy and asked about side effects of the antiemetic medications received.

Quality of Life (QOL) was evaluated through the Functional Living Index of Emesis (FLIE)[13]. The FLIE questionnaire consists of an 18 items. Nine of these items refer to nausea and nine to vomiting. These questions attempt to assess the impact of CHTEM on the patients' daily functioning in the psychological, social and physical spheres[13]. Since we excluded patients who had any nausea or vomiting before study entry and only studied chemotherapy naive patients, this questionnaire was applied only once to all subjects at 24 hours after study entry to evaluate the impact of nausea and vomiting induced by chemotherapy at the completion of the study. The data were collected through a specially designed database program CARE® kindly provided by Smith Kline Beecham.

We employed the Chi-square with Yates correction or Fisher exact tests to analyze discrete variables and ANOVA for continuous ones. Only two-tailed p values were considered. We used Kaplan Mayer curves and Mantel-Haenszel test to compare the times of freedom from nausea and vomiting. Sample size was set at 80 patients as to detect, assuming a type 1 error of 0.05 and a type 2 error of 0.20, a 30% difference in antiemetic potency between the two treatment arms.

Results

The clinical characteristics of the 80 patients studied are depicted in table 1. Thirty five patients were randomized to OND and 45 to GRA. There was no significant differences regarding age, sex, alcohol consumption, primary sites of the tumor, and emetogenic potential of the chemotherapy received between the patients treated with GRA or OND. Although there was a trend for superiority of OND for CCV (RR = 0.68; 95% CI 0.46 to 1.0; p = 0.08) and CCNV (RR = 0.63; 95% CI 0.37 to1.06; p = 0.08), these differences did not reach statistical significance. In addition no statistical significant differences were observed

Acta Oncol. Bras. Vol. 20 - nº 03, 121-126, jul-ago-set, 2000

between both groups of patients regarding CCN, number of vomiting episodes, reported nausea intensity, and FLIE scores. Furthermore, when the aforementioned parameters were analyzed within the groups of patients treated with highly or moderately emetogenic chemotherapy regimens, again no significant differences were found between the subgroups of patients assigned to GRA and OND (table 2).

OND showed a tendency to prolong the time of freedom from nausea when compared with GRA (p = 0.06). There was, however, no significant difference of the time of freedom from vomiting between the two antiemetic drugs (p = 0.38) (figure 1). Both anti-emetic agents were well tolerated and table 3 shows the toxicities observed for both groups of patients. Constipation was significantly more common in the group of patients treated with OND (p = 0.003). No other significant differences regarding somnolence, diarrhea or headache were observed between the groups of patients treated with GRA or OND.

Table 1 - Clinical characteristics of the patients studied

	Granisetron (n=45)	Ondansetron (n=35)	p
Sex			
Male	15	8	0,51
Female	32	27	
Age (mean)	51,8	48,1	0,23
Weight (mean)	61,4	61,2	0,94
Alcohol consumption			
≤ 5 doses/week	37	33	0,20
≥ 6 doses/week	8	2	
Primary site of tumor			
Breast	24	21	0,71
Lung	7	4	
Head and neck	2	3	
Ovary	2	3	
Bladder	2	2	
Testes	3	1	
Others	5	1	
Emetogenic potential			
Moderate	24	21	0,71
High	21	14	

Table 4 shows the acquisition costs of these two antiemetic medications at the doses utilized in this study. This figure was expressed as a percentage of the acquisition costs of the chemotherapy regimens used for the treatment of the most common solid tumors seen at our center. The acquisition costs of OND were higher when compared with GRA in the dosage used in this study. Furthermore, OND acquisition costs represented a higher percentage of the total acquisition costs of all the chemotherapy regimens most commonly used at our institution. These differences of total acquisition costs for the anti-emetic agents studied for the first cycle of treatment would certainly be magnified when we consider an average of six cycles of each of the aforementioned regimens per patient.

Table 2 - Complete control of vomiting (CCV), nausea (CCN), nausea and vomiting (CCNV), number of vomiting episodes (NV), mean nausea intensity (MNI), and FLIE questionnaire scores (FLIE) of patients treated with OND and GRA. Results for the subgroups of patients treated with moderately emetogenic and highly emetogenic chemotherapy regimens are also reported. NV and MNI are reported only for patients who experienced vomiting and nausea, respectively

	ALL PATIENTS			HIGHLY EMETOGENIC			MODERATELY EMETOGENIC		
Treatments	OND(%)	GRA (%)	P	OND (%)	GRA (%)	P	OND (%)	GRA (%)	P
N	35	45		14	21		21	24	
CCV	68,57	46,6	0,08	85,70	57,14	0,15	57,14	37,5	0,30
CCN	45,7	40	0,77	64,28	47,61	0,53	33,3	33,3	0,75
CCNV	42,85	22,2	0,08	64,28	33,3	0,14	28,57	12,5	0,26
Number of* vomiting episodes	2,81	4,04	0,26	1,0	2,22	0,47	3,22	5,13	0,13
Intensity** of nausea	3,19	3,28	0,84	2,78	3,07	0,73	3,43	3,43	0,87
FLIE scores	41,25	54,04	0,11	35,28	41,23	0,57	45,23	65,20	0,08

*Considering only patients who vomited

**Considering only patients who had nausea

Acta Oncol. Bras. Vol. 20 - nº 03, 121-126, jul-ago-set, 2000

Table 3 - Toxicites observed among patients treated with Granisetron (GRA) and Ondasetron (OND).

Toxicity	GRA (%) N = 45	OND (%) N = 35	p
Headache	37,8	31,4	0,72
Somnolence	8,9	17,1	0,44
Diarrhea	6,7	11,7	0,72
Constipation	0	11,4	0,03
Xerostomia	11,1	8,6	1

Discussion

In this study, we attempted to compare the antiemetic potency and the impact in the QOL in the first 24 hours after chemotherapy administration of two antiemetic regimens. A standard but more expensive dose of 32 mg IV of OND[13] was compared with the lowest effective dose of GRA[5,11] described in the literature. Both medications were administered as a single intravenous bolus 30 minutes prior to moderately or highly emetogenic chemotherapy on a double-blinded fashion. Despite a tendency for OND superiority in CCV and CCNV (p = 0.08 for both), we were unable to disclose a statistically significant difference in antiemetic efficacy in terms of CCN, number of vomiting episodes, and nausea intensity. Furthermore, no statistically significant differences were detected when the aforementioned endpoints were evaluated within the groups of patients treated with moderately or highly emetogenic chemotherapy regimens.

Navari et al.[5] compared the efficacy of similar doses of intravenous GRA and OND without corticosteroids in a series of 987 patients who received cisplatin-based chemotherapy regimens. These authors also noted no significant difference in antiemetic potency between these two drugs. However, in their study, Navari et al used a fractionated schedule of 3 doses of 0.15 mg/kg of OND given 4 hours apart, which, according to another study[12], may be inferior to the entire dose of OND given at once prior to chemotherapy. This difference in the schedule of administration of OND may explain the trend that we observed in our study favoring OND over GRA. In

Figure 1

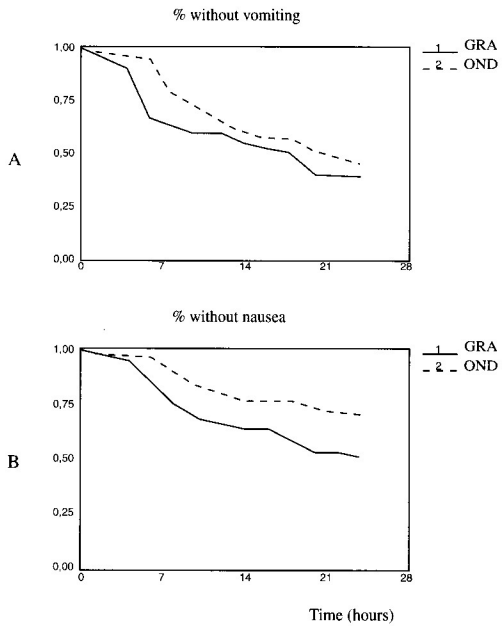

Figure 1. Time to first episode of vomiting (TTV) (A) and nausea (TTN) (B) episodes. GRA is represented by continuous line and (1) and OND by broken line (2)

Table 4 - Acquisition costs of Granisetron 1 mg vials and Ondansetron 8 mg vials and of the antineoplastic chemotherapy regimens, considered highly or moderately emetogenic, used at our institution for the most common solid tumors. Official Brazilian market prices were converted to US$ dollars for Ondansetron (Zofran®) and Granisetron (Kytril®). For chemotherapy drugs acquisition costs calculation, we considered the mean body surface area of 1.64 obtained from the patients enrolled in this study. The official Brazilian market prices were utilized and we expressed the cost of one dose of each of the antiemetic regimens used in this study as a percentage of the total acquisition costs of the chemotherapy regimens. FLP: fluorouracil, low dose leucovorin and cisplatin; CMV: cisplatin, methotrexate and vinblastine; FAC: fluorouracil, doxorubicin and cyclophosphamide; PEB: cisplatin, etoposide and bleomycin; PE: cisplatin and etoposide; CP: cyclophosphamide and cisplatin.

	U$	Head/Neck (FLP)	Bladder (CMV)	Breast (FAC)	Testes (PEB)	Lung (PE)	Ovary (CP)
RC (U$)*	484	388	260	856	332	236	
GRA (Kytril®)	32,8	6,7%	8,4 %	12,5%	3,8%	9,86%	13,89%
OND 32mg (Zofran®)	160	33,02 %	41,18 %	61,32%	18,66%	48,07%	67,72%

*Chemotherapy regimen acquisition costs (RC) in U$

support to Navari et al.[5], we also found a decreased efficacy of both antiemetics in the group of women treated with doxorubicin-based moderately emetogenic chemotherapy regimens when compared with the group of patients treated with highly emetogenic chemotherapy that also included men.

When we analyzed the time to the first episode of nausea (TTN) and time to the first episode of vomiting (TTV), a trend favoring OND over GRA was observed, specially in terms of TTN ($p = 0.06$). In contrast Navari et al. [5] did not describe such a difference in terms of TTN or TTV. It is conceivable that this difference in effect may be related to the different OND administration schedule employed by those authors.

The data from randomized trials that have compared OND and GRA (2-10) suggest that there is no difference in efficacy between these two agents. Therefore, the acquisition (purchase) costs as well as the impact in the QOL of the patients who receive these medications as prophylaxis against CHTEM may assume an important role in the decision whether to choose one of them over the other.

In order to explore the impact in the QOL of our patients treated with OND or GRA, we employed the FLIE questionnaire[13]. This instrument, by its multidimensional characteristics, evaluates social, psychological and physical well-being of patients treated with emetogenic chemotherapy. We evaluated patients after 24 hours of having received chemotherapy and we found no statistically significant differences in the FLIE scores obtained between patients treated with GRA and OND.

Several investigators analyzed the economic costs of CHTEM[14,15]. The total costs of CHTEM prophylaxis, according to these studies, include those related to acquisition of these drugs, their preparation and administration to patients both prophylactically and as rescue medications for nausea and/or vomiting episodes. Furthermore, the time spent in the unit, costs of cleaning up the patients and the unit after an emetic episode and of hospital admissions that may be required for the treatment of severe CHTEM are also important considerations in the total costs involved in CHTEM prophylaxis.

We can assume that the acquisition costs of GRA and OND are the main determinants of the total costs differences of these treatments in this study. We can arrive at this conclusion because in our study: a) no patient required admission in the first 24 hours because of nausea and vomiting; b) there were no differences in the preparation and administration costs for OND and GRA since both were given as a single IV infusion before chemotherapy, c) rescue antiemetics were handled to patients to be taken orally if necessary for nausea and/or vomiting at home without any additional pharmacist or nursing related costs for their administration and d) the costs of rescue antiemetics used in this study were quite low. Therefore, GRA at the dose used in this study seems to be the most cost-effective option as can be seen in table 4.

It is important to note that this study has limitations. Since this study analyzed only acute CHTEM, we cannot extrapolate these results for delayed CHTEM prophylaxis. Furthermore, since only a small number of patients were studied, a smaller but clinically significant difference in antiemetic efficacy between both arms may have probably gone undetected in this study. Additionally, unlike when we first devised this study, it is widely accepted now that corticosteroids should be routinely incorporated to Serotonin antagonists for CHTEM prophylaxis[16]. Our new studies will incorporate corticosteroids which acquisition costs are low and may, by increasing the antiemetic efficacy of both GRA and OND, further decrease the trend that we observed favoring OND over GRA in this study.

In conclusion, in spite of a trend favoring OND over GRA in terms of antiemetic efficacy at the doses utilized in this study, no significant differences emmerged in the QOL evaluated through the FLIE questionnaire between both arms. Therefore, GRA at dose of 10 μg/kg may be an acceptable and cost-effective alternative for acute CHTEM prophylaxis when compared with the standard and more expensive treatment of OND at the dose 32 mg. This is a particularly important issue for institutions from developing countries, where the financial resources for health care may be limited.

Resumo

Os antagonistas serotoninérgicos como o Granisetron (GRA) e Ondansetron (OND) são medicações antieméticas eficazes porém muito custosas. Neste estudo, comparamos a eficácia antiemética da menor dose endovenosa (EV) recomendada de GRA (10 μg/kg) com a dose padrão e mais cara de 32 mg EV de OND administradas antes de quimioterapia de alto e moderado poder emetogênico a pacientes previamente não tratados. Oitenta pacientes foram aleatorizados, 45 para GRA e 35 para OND. Ambos os grupos foram comparáveis em relação a idade, sexo, uso de álcool e poder emetogênico da quimioterapia administrada. A eficácia destas medicações foi medida 24 horas após a sua administração. Proteção completa de vômitos, náuseas e ambos náuseas e vômitos ocorreram em 68,5 versus 46.6% ($p = 0.083$), 45% versus 40% ($p = 0.77$) and 42% versus 22 % ($p = 0.08$) dos pacientes tratados com OND e GRA, respectivamente. Não houve diferenças significativas entre os dois grupos em relação ao número de episódios de vômitos, intensidade da náusea, e na avaliação de qualidade de vida (QV) medida através do questionário FLIE ("Functional Living Index of Emesis"). O custo de aquisição do regime contendo GRA foi cerca de 5 vezes inferior ao de OND. Concluímos que, apesar de uma tendência favorecendo uma maior eficácia antiemética de OND, face à grande diferença em termos do preço de aquisição de ambos os regimes antieméticos, a utilização de GRA na dose de 10 μg/kg EV parece ser uma alternativa aceitável à mais custosa dose padrão de 32 mg EV de OND, sem prejuízo na avaliação de QV.

Acta Oncol. Bras. Vol. 20 - nº 03, 121-126, jul-ago-set, 2000

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