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Effectiveness of cyproheptadine in the management of delayed vomiting after cisplatin-based chemotherapy and the assessment of the influence of cyproheptadine on quality of life

Piotr Koralewski, Iwona Nawara, Maria Marczak-Ziętkiewicz, Wojciech Cegielski

Introduction. Nausea and vomiting belong to the most frequently occurring side effects of chemotherapy, significantly worsening the quality of life of patients receiving cytostatics. The problem of treatment of delayed emesis occurring after administration of cytostatics with the highest emetic potential remains unsolved.
Cyproheptadine is a non-specific blocker of serotonine and histamine receptors with a proven antiallergic, antiulcerous and appetite stimulating activity. Its non-specific influence on central and peripheral serotonine receptors suggests the possible influence of this drug on emesis in patients.
The aim of this study was to assess the effectiveness of cyproheptadine in the management of delayed vomiting after the cisplatin-based multi-drug chemotherapy and to assess the influence of cyproheptadine on the quality of life of patients receiving chemotherapy.
Material and methods. The study was prospective and randomized. Sixty chemotherapy-naïve patients (44 women and 16 men), for whom at least three courses of cisplatine-based chemotherapy were planned, were entered. All patients received standard antiemetic treatment (ondansetron /8 mg iv/ or tropisetron /5 mg iv / with dexamethazone /8 mg iv / during the 1st day of treatment and also during the 2nd day when symptoms of nausea and vomiting ECOG grade 2 persisted). The patients belonging to one group additionally received cyproheptadine (Peritol – EGIS™) 12 mg per day for subsequent courses. To compare differences between studied groups according to intensity of nausea and vomiting, non-parametric Mann-Whitney's and chi-square tests were applied. The remaining parameters (body weight, level of physical and psychological functioning) were analyzed with the use of t-Student test and F Snedecor's test.
Results. The study did not confirm the hypothesis about the influence of cyprohepatdine on the frequency and intensity of delayed vomiting after chemotherapy. However a positive influence of cyproheptadine administration on the occurrence of delayed nausea, body weight gain and quality of life in the aspect of physical functioning was observed.

Ocena skuteczności cyproheptadyny w leczeniu wymiotów opóźnionych, towarzyszących chemioterapii, z udziałem cisplatyny i jej wpływ na jakość życia chorych poddanych chemioterapii

Wstęp. Wymioty i nudności są najczęściej występującymi niepożądanymi objawami chemioterapii, są też objawami istotnie pogarszającymi jakość życia chorych poddanych leczeniu cytostatykami. Problem leczenia wymiotów opóźnionych, występujących po zastosowaniu cytostatyków należących do grupy o najsilniejszym działaniu emetogennym, pozostaje ciągle otwarty.
Cyproheptadyna jest niespecyficznym blokerem receptorów serotoninowych i histaminowych o udowodnionym działaniu w leczeniu alergii, przeciwwrzodowym i zwiększającym łaknienie. Niespecyficzne działanie cyproheptadyny na receptory serotoninowe centralne i obwodowe sugeruje możliwość wpływu tego leku na występowanie u pacjentów nudności i wymiotów.
Celem pracy były ocena skuteczności cyproheptadyny w opanowywaniu nudności i wymiotów opóźnionych w grupie chorych poddanych chemioterapii wielolekowej z udziałem cisplatyny oraz ocena wpływu leczenia z udziałem cyproheptadyny na jakość życia chorych poddanych leczeniu chemicznemu.
Materiał kliniczny i metodyka badania. Doświadczenie miało charakter prospektywnie zaplanowanej, randomizowanej próby klinicznej. Do badania zakwalifikowano 60 chorych (44 kobiety i 16 mężczyzn), którzy otrzymali trzy pełne serie chemioterapii wielolekowej, opartej o cisplatynę. Wszyscy chorzy otrzymywali standardowe leczenie przeciwwymiotne

Chemotherapy Dept. Rydygier Memorial Hospital, Cracow, Poland

drogą dożylną tj. ondansetron (8 mg) lub tropisetron (5 mg) z deksametazonem (8 mg) w pierwszym dniu leczenia i ewentualnie w dniu kolejnym w przypadku utrzymywania się nudności i wymiotów drugiego stopnia wg ECOG, a jedna z grup dodatkowo otrzymywała pomiędzy kolejnymi seriami leczenia cyproheptadynę w dawce 12 mg/dobę. Metody statystyczne. W celu porównania różnic pomiedzy badanymi grupami w zakresie natężenia nudności i wymiotów użyto testów nieparametrycznych Manna-Whitneya i chi-kwadrat. Do analizy statystycznej pozostałych cech (masa ciała, poziom funkcjonowania psychologicznego i fizycznego) wykorzystano test t-Studenta oraz test F Snedecora.
Wyniki. Badanie nie potwierdziło hipotezy o wpływie cyproheptadyny na częstość i nasilenie wymiotów opóźnionych po chemioterapii. Wykazano natomiast pozytywny wpływ tego rodzaju leczenia na zmniejszenie nasilenia nudności, przyrost wagi ciała, a także samopoczucie fizyczne, rozumiane jako jeden z wymiarów jakości życia chorych.

Key words: cyproheptadyna, nudności i wymioty opóźnione, chemioterapia oparta o cisplatynę, jakość życia
Słowa kluczowe: cyproheptadine, delayed emesis, cisplatin-based chemotherapy, quality of life

Introduction

Nausea and vomiting belong to the most frequently occurring side effects of chemotherapy, significantly worsening the quality of life of patients receiving treatment with cytostatics.[1, 2]. Cisplatine belongs to cytostatics with the highest emetic potential. The problem of acute emesis was solved by applying the strategies of concomitant administration of 5-HT3 receptors antagonists together with dexamethasone, on the contrary the problem of treatment of delayed emesis remains unsolved. [3, 4]. Delayed emesis are defined as emesis occurring 24 hours after chemotherapy. About 20–50% of patients treated with cisplatine still suffer from this adverse reaction.

The underlying cause of delayed emesis is not clear. The influence of cytostatics or its metabolite on the gut or central nervous system and so called rebound effect, occurring after the activity of antiemetics stops, are listed as possible causes [5, 6, 7]. It can be also suspected, that neurotransmitters and receptors other than 5-HT3 take part in pathogenesis of delayed emesis.

Cyproheptadine is a non-specific blocker of serotonine and histamine receptors with a proven antiallergic, antiulcerous and appetite stimulating activity [8]. Its non-specific influence on central and peripheral serotonine receptors suggests the possible influence of this drug on emesis in patients. At the same time its 5-HT2 receptor antagonist effect decreases the secretion of hydrochloric acid in stomach. The sedating effect – through blockade of histamine (H3) receptors – can also have a favorable result in decreasing nausea and vomiting (benzodiazepins and chlorpromazine are often used in antiemetic procedures). On account of what mentioned above it seems justifiable to conclude that administration of the drug with a multiple mechanism of action, blocking central and peripheral receptors can lead to a better tolerance of chemotherapy.

The end points of this study were:
– the assessment of effectiveness of cyproheptadine in the management of delayed vomiting after the cisplatin-based multi-drug chemotherapy,
– the assessment of influence of cyproheptadine on the quality of life of patients treated with chemotherapy.

Material and methods

The study was prospective and randomized. 60 chemotherapy-naïve patients (44 women and 16 men), for whom at least three courses of cisplatine-based chemotherapy were planned, were entered.

The population of patients was divided into two groups A and B with same number of patients. The randomization was based on the date of birth: even number – group A, odd number – group B. All patients received cisplatine-based multi-drug chemotherapy and identical antiemetic treatment (ondansetron /8 mg iv/ or tropisetron /5 mg iv/ with dexamethazone /8 mg iv / during the 1st day of treatment and also during the 2nd day when symptoms of nausea and vomiting ECOG grade 2 persisted). The patients belonging to group A additionally received cyproheptadine (Peritol – EGIS™) 12 mg per day for subsequent courses.

Mean age in group A was 54.9 years (34–73 years) and in group B – 57.2 years (41–72 years). Table I summarizes the information about diagnosis and applied treatment for all patients entered in the study. Frequency and intensity of nausea and vomiting were analyzed with the patients' diaries of side effects of chemotherapy. Each course was assessed separately with ECOG scale.

Tab. I. Clinical material according to diagnosis and treatment procedures (in brackets number of patients in group A+B)

Diagnosis	Treatment				
	PC	GEM+DDP	5FU+DDP	BEP	Together
Ovarian cancer	44 (22 + 22)				44 (22 + 22)
Lung cancer		8 (4 + 4)			8 (4 + 4)
Head and neck cancers			7 (3 + 4)		7 (3 + 4)
Testicular cancer				1 (1 + 0)	1 (1 + 0)
Together	44 (22 + 22)	8 (4 +4)	7 (3 + 4)	1 (1 + 0)	60 (30 + 30)

The quality of life of patients was evaluated according to Rotterdam Symptom Checklist, applied to check the level of psychological and physical functioning disturbances [9].

The control measurements of body weight were also performed during the study.

The observation of frequency and intensity of nausea and vomiting applied to all three courses of chemotherapy so three records in patients' diaries were obtained (Ist after 1st course, IInd after 2nd etc), while the quality of life was assessed before the treatment (point „0") and then after each course (4 measurements).

Statistical analysis

For the following parameters statistical analysis was performed: vomiting, nausea, level of physical and psychological functioning and body weight.

Intensity of nausea and vomiting were ordinal variables of integer values. Non-parametric Mann-Whitney's and chi-square tests were applied to compare differences between studied groups.

Body weight is a continuous interval parameter. Level of physical and psychological functioning as a sum of multiple factors can be assumed to be (according to Central Limit Theorem) variables with near-normal distribution.

t-Student test for non-related variables was applied in order to establish significance of differences of mean values of parameters in a given measurement between groups A and B. Significance was assumed for P values <0.05.

In order to establish significance of differences of means in one group (A or B) but in different time-points, one-way ANOVA for related variables was applied (F Snedecor's test). Usage of both tests was justified by results of Kołmogorow--Smirnow' test of normal distribution of analyzed data.

Results

Statistical analysis of the data from patients' diaries comparing the number of observed side effects i.e. nausea and vomiting in the period from the 2nd till the 9th day after chemotherapy did not reveal any significant differences between both groups in case of vomiting. Calculated statistics value (Mann-Whitney's test) equals –1.38 with p value of 0.17.

On the other hand significant influence of cyproheptadine administration on the occurrence of delayed nausea was observed. Value of chi-square statistics equals 4.4, what with one degree of freedom means statistical significance on the level of 0.05 (p=0.036).

From qualitative analysis of cards of observation it can be concluded that cyproheptadine is well tolerated by patients treated with cytostatics.

The results of quality of life measurements obtained with the Rotterdam Symptom Checklist indicate that both the physical and psychological well-being remained more stable in patients from the group A (receiving cyproheptadine) than in the group B (low values of standard deviation).

The patients from group A rated their physical functioning better during subsequent courses of chemotherapy. No difference was observed however, according to psychological functioning of patients in both groups.

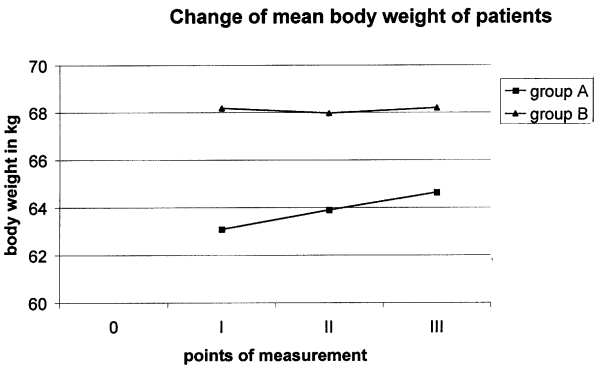

Fig. 1. Change of mean body weight of patients

Tables II and III show the results of comparison of mean values indicating the level of functioning disturbances in psychological and physical aspects.
The increase of body weight measured during the treatment is presented on Figure 1.

Tab. II. The comparison of mean values of levels of psychological functioning disturbances in groups A i B and in subsequent points of evaluation (0-before chemotherapy, I – 1st course, II – 2nd course, III – 3rd course)

Point of evaluation		Group A		Group B		Results of t-Student test for groups A and B		
		Mean	Standard deviation	Mean	Standard Deviation	Value of t-statistics	No. of degree of freedom	p
0		13.70	4.15	14.13	4.26	-0.399	58	>0.05
I		11.60	2.62	11.80	3.38	-0.256	58	>0.05
II		10.90	2.17	10.93	3.10	-0.048	58	>0.05
III		10.50	1.81	11.40	3.27	-1.320	58	>0.05
Value of F statistics in ANOVA between measurements	Value of F statistics	9.879		12.855				
O,I,II,III	Number of degree of freedom	3		3				
	p	<0.001		<0.001				
Value of F statistics in ANOVA between measurements	Value of F statistics	2.592		1.918				
I,II,III	Number of degree of freedom	2		2				
	p	>0.05		>0.05				

Tab. III. The comparison of mean values of physical well being disturbances in group A and B and in subsequent points of evaluation (0-before chemotherapy, I – 1st course, II – 2nd course, III – 3rd course)

Point of evaluation		Group A		Group B		Results of t-Student test for groups A and B		
		Mean	Standard deviation	Mean	Standard Deviation	Value of t-statistics	No. of degree of freedom	p
0		25.60	4.69	26.23	5.32	-0.489	58	>0.05
I		25.83	3.39	28.10	6.42	-1.636	58	>0.05
II		24.87	4.60	27.47	6.87	-1.723	58	>0.05
III		24.53	3.61	27.00	5.41	-2.077	58	<0.05
Value of F statistics in ANOVA between measurements O,I,II,III	Value of F statistics	1.028		1.289				
	Number of degree of freedom	3		3				
	p	>0.05		>0.05				
Value of F statistics in ANOVA between measurements I,II,III	Value of F statistics	1.455		0.949				
	Number of degree of freedom	2		2				
	p	>0.05		>0.05				

The mean body weight of patients from group B is higher in every checked time-point than of patients from group A. Those differences though are not statistically significant due to relatively high value of standard deviation of this variable in both groups.

In group A the mean body weight systematically increases during subsequent measurements. In group B there is a small drop between points I and II, and then minimal improvement.

As a result of analysis of variance for related data it was shown that in group A body weight gain between separate measurements is significant with p=0.05 (F test value = 3.381) while group B was lacking such relationship (respective value of F = 0.095).

Summary

Broad and non-typical spectrum of activity of cyproheptadine allowed the hypothesis that this drug can be effectively administered to treat emesis occurring after 24 hours after chemotherapy. The paper by Andersen et al. [10] indicating the effectiveness of cyproheptadine in the treatment of cyclic vomiting syndrome in children can indirectly justify this assumption.

The influence on final results of such parameters as sex, age and possible tendency to alcohol abuse was eliminated by the construction of the study.

Statistical description of collected clinical data did not confirm the expected influence of the drug on frequency and intensity of delayed vomiting. Significant decrease of nausea, confirming the activity of the drug, was observed however, the effect was not as good as expected. It can not be excluded, that rising the dose of cyproheptadine can enhance its effectiveness, but still there is not enough clinical data to support this thesis.

Relatively low price of the drug allows its prolonged administration. This encouraged authors to perform the analysis on its influence on quality of life of patients treated with chemotherapy. The attempt to translate subjective qualitative data into the language of statistics was undertaken. Finally, it was confirmed with statistical significance, that the differences in the aspect of physical functioning in favor of group treated with cyproheptadine are observed after three months of use of the drug. The stable tendency to body weight gain in patients receiving this drug supports this observation. Differences on the level of psychological functioning were not significant.

However it is understood, that the weak point of this study is the lack of double-blind method with the use of placebo, it still seems reasonable to perform further studies on cyproheptadine in concomitant therapy for patients treated with anticancer chemotherapy. Continuous improvement of quality of life of patients suffering from neoplastic disease should form a superior goal. It is also advisable to search for new, better methods for evaluating the quality of life itself, one of the most complex and complicated issues in medicine.

Conclusions

1. The administration of cyproheptadine at the dose 12 mg/day between subsequent courses of cisplatine based chemotherapy does not influence occurrence of delayed vomiting.
2. Administration of the drug decreases frequency and intensity of delayed nausea.

3. The quality of life in physical aspect of patients receiving cyproheptadine is better than in the control group.
4. Existing observations justify the introduction of new studies on application of cyproheptadine as an adjunctive therapy for patients treated with anticancer chemotherapy.

Piotr Koralewski M.D. Ph.D
Chemotherapy Dept. Rydygier Memorial Hospital
Os. Złotej Jesieni 1
31-826 Cracow, Poland

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