Comparison of ondansetron-dexamethasone with metoclopramide-dexamethasone in the control of cisplatin induced emesis

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Ondansetron (5 hydroxytriptamine receptor antagonist) plus dexametha sone have been compared with metoclopramide plus dexamethasone in the control of emesis induced by cisplatin. A total of 88 patients with lung carcinoma were involved in the study. These patients received cisplatin (80 mg/m²/d) at different combinations. Forty-four patients received ondansetron plus dexamethasone and 44 patients received metoclopramide plus dexamethasone for antiemetic prophylaxis. Complete control was achieved in 45.5% of ondansetron patients and in 29.5% of metoclopramide patients ($p<0.05$). Complete plus major responses were achieved in 81.9% of ondansetron group and 61.3% of metoclopramide group ($p<0.01$). This difference was statistically significant in the control of acute emesis (24h). However there was no significant difference between ondansetron group and metoclopramide group in the control of delayed emesis. Both antiemetic schedules were well tolerated. The control of acute emesis was superior in patients treated with ondansetron plus dexamethasone than the other group. But the role of ondansetron in the control of delayed emesis required further study. [Turk J Med Res 1993, 11(3): 131-135]

Key Wods: Ondansetron, Metoclopramide, Dexamethasone, Emesis

Cisplatin, which is an ematogenic agent has side effects like vomiting and nausea as other cytotoxic drugs. In the control of emesis induced by cisplatin ondansetron [5 HT3 (hydroxytriptamin receptor)] is widely used and 30-55% complete emetic control is achieved (1).

Recent researches indicate that ondansetron is less toxic with respect to metoclopramide. Duo to the lack of antidopaminergic activity and extrapramidal reaction all attentions are focused on ondansetron.

Corticosteroids increase the effect of metoclopromide in the emesis induced by chemotherapy (5,6,14,18). The similar synergic effects are also observed in the combination of ondansetron and corticosteroid (1,7,8,12,13).

The purpose of this study is to compare ondansetron plus dexamethasone with metoclopramide plus dexamethasone in the control of emesis induced by cisplatin.

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MATERIALS AND METHODS

In this study 88 patients with lung carcinoma were subjected. All patients received cisplatin combined chemotherapy. The study population was divided into two equal groups. Fourty-four patients received ondansetron plus dexamethasone while the rest received-metoclopramide plus dexamethasone as antiemetic therapeutic. ECOG classification was used for the patient performance. The specifications of the patients were given in Table 1.

All patients received cisplatin in single dose (80 mg/m²) at five different combinations. None of the patients had chronic alcohol habbit, vomiting-nausea due to other organic reasons, psychological disorders and cardiovascular or cerebrovascular defects.

Before applying cisplatin, antiemetic treatment was started. In the ondansetron group, 8 mg. ondansetron plus 20 mg dexamethasone IV were applied. Following to this treatment 8 mg ondansetron IV was applied in every four hours. At the twelveth hour oral ondansetron (8 mg) has been started. Therefore at the end of first 24 hours 32 mg of ondansetron had been applied to the patients. The antiemetic treatment was applied to the patients for five days with 8 mg ondan-

Table 1. Specifications of the study group

	Ondansetron	Metoclopramide
Number of the patients	44	44
Male	38	42
Female	6	2
Age Average	52	54.85
The youngest	29	19
The oldest	76	69
Age > 60	10	17
Age < 60	34	27
Average cisplatin dosage	128,4	134,45
Dosage over 90 mg.	41	42
Dosage below 90 mg.	3	2
Performance state		
0-1	41	40
2	3	4
Cell Type		
Small cell	14	13
Squamous cell	12	15
Adenocancer	17	15
Big cell	1	1
Chemotherapies		
VC	15	20
MIC	8	4
MVC	6	9
VIC	9	6
VCE	6	6

V:Vepesid, C:Cisplatin, M:Mitomycin, hlfosfamid, E:Epirubicine

setron in every 12 hours. In the metoclopramide group; 20 mg metoclopramide plus 20 mg dexamethasone were given thirty minutes before the cisplatin therapy. After this period, 3 dose in every 2 hours and latter 3 dose in every 3 hours metoclopramide IV was applied (Dose; 2 mg/kg/day). After the first 24 hours; 10 mg metoclopramide applied in every six hours for five days.

Vomiting and nausea, rised in the first 24 hours were named as acute emesis and emesis rised after this period called as delayed emesis. Every nausea-vomiting was classified as an emetic attack and validated numerically.

O emetic attack *m* Complete response,

1-2 emetic attack -• Major response,

3-5 emetic attack -» Minor response,

More than 5 emetic attacks were accepted as unsatisfactory response. The emetic attacks in the first 24 hours were recorded by the doctors, and then the patients were asked to fill the files about their attacks during they stayed at hospital. When the patients were applied for the next chemotherapy, they were all questioned about the emetic attacks.

RESULTS

In our study fourty-four patients received metoclopramide plus dexamethasone and the rest of the patients received ondansetron plus dexamethasone for antiemetic prophylaxis during five days (Table 1). By the emetic prophylaxis chemotherapy was tolarated. In the first 24 hours after chemotherapy 45.5% of the patients in the ondansetronplus dexamethasone group and %29.5 of the patients in the metoclopramide plus dexamethasone group didn't have emetic attack. These results indicate that a statistically significant complete control were achieved by using ondansetron ($p<0.05$). Satisfactory (complete+major) responses were achieved in 81.9% in ondansetron group and 61.3% in metoclopromide group ($p<0.01$). During the acute period, patients with more than 5 emetic attacks in ondansetron group was 6.8% while in metoclopramide group the percentage was 22.7% ($p<0.01$). So in the control of acute emesis, ondansetron plus dexamethasone has a significant effect (Table 2, Fig. 1).

However the results are not the same in the delayed emesis. The complete response in the second day were about 47.7% in ondansetron group and 66% in the metoclopramide group

Table2. Control of acute emesis ondansetron-dexamethasone and metoclopramide-dexamethasone

Responses	Ondansetron		Metoclopramide		
	No	%	No	%	
Complete	20	45.5	13	29.5	p<0.06
Majör	16	36.4	14	31.8	
Minor	5	11.3	7	16	
Unsatisfactory	3	6.8	10	22.7	p<0.01
Satisfactory (Complete+Major)	36		27	61.3	p<0.01

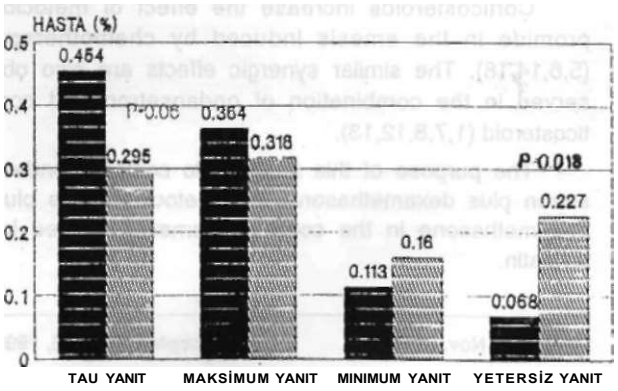

Figure 1. Comparison of the ondansetron and metoclopramide in the control of acute emesis.

Table 3. **Comparison of the responses in the late emesis control by ondansetron and metoclopramide**

Responses	2nd day		3th day		4th day		5thday	
	No	%	No	%	No	%	No	%
Complete								
OND	21	47.7	33	75.1	42	95.5	44	100
MET	29	66	36	81.8	41	93	44	100
	p<0.04		p<0.21		p<0.32			
Maximal								
OND	16	36.4	5	11.3	2	4.5	—	—
MET	9	20.5	4	q p	q	7f)		
				*t.e.				
Minimal								
OND	6	13.6	5	11.3	—	—	—	—
MET	4	9	2	4.5	—	—	—	—
Unsatisfactory								
OND	1	2.3	1	2.3				
MET	2	4.5	2	4.5				

Table 4. Comparison of the complete+maximal responses in the control of late emesis

	2nd day		3th day		4th day	
	No	%	No	%	No	%
OND	37	84.1	38	86.4	44	100
MET	38	86.5	40	91	44	100
	p<0.38		p<0.25			

(p<0.04). So metoclopramide was statistically significant in delayed emesis (Table 3). The complete plus major response in ondansetron group was 84.1% and in metoclopramide group it was 86.5%, but this difference was statistically insignificant (Table 4).

In the thirth day complete responses for ondansetron-dexamethasone was 75.1% while for metoclopramide-dexamethasone was 91%. This difference was statistically insignificant to (p<0.25).

The complete responses were achieved with both groups in the fourth day. For ondansetron-dexamethasone group the percentage was 95.5 while for metoclopromide-dexamethasone it was 93 (p<0.32) (Table 3,4 and Fig 2).

Six patients from metoclopramide had elevated transaminase levels and one patient complained from headache. None of the patients had extraprimidal symptoms (Table V). In the ondansetron-dexamethasone group 9 patients had elevated serum transaminase level however as in the metoclopromide-dexamethasone group; this elevation didn't exceed the double fold. One patient had hypotensive attack 2 patients complained about sleeping disorders and 4 patients had headache.

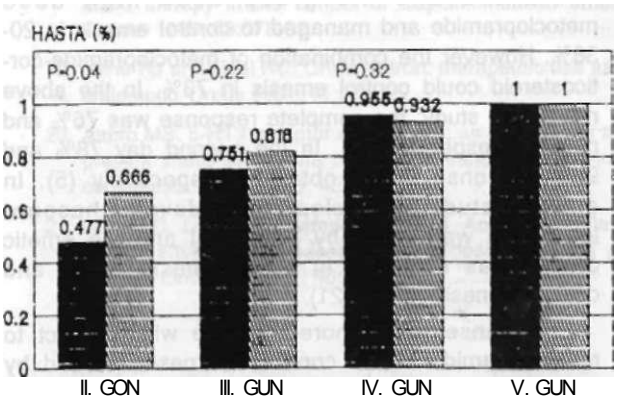

Figure 2. Comparison of ondansetron and metoclopramide in the control of late emesis.

DISCUSSION

Emetic center is a chemoreceptor trigger zone which is placed in the area postrema of the fourth ventricule. It can be effected from materials present in blood or cerebrospinal fluid. Nausea and vomiting are caused

Table 5. Side-effects in both groups

Side effect	OND		MET	
Enzyme elevation	9	(%20.5)	6	(%13.5)
Headache	4	(%5)	1	(%2.3)
Hypotension	1		—	
Spleeping	2		—	
Total	16	(%36.4)	7	(%15.9)

due to the secretion of serotonin from GIS and the activation of the splancnic afferent nerves. The chemotherapeutic agents cause to the increase of serotonin in both blood and cerebrospinal fluid, which results to vomiting and nausia (8,10,18,19,20).

High dose metoclopromide inactivates serotonin receptors so prevents nausia and vomiting but its antidopaminergic effects cause extrapramidal symptoms (6,7,8,10,18,19,20).

Since ondansetron binds to 5TH (5 hydroxytriptamine) receptor, it does not have distonic effec. Therefore, it has a good antiemetic property (1,9,10,19,20).

It is known that corticosteroids induce the antiemetic property of both metoclopramide and ondansetron (5-8,12,14,18,20,21). Although the exact effective mechanism of corticosteroids is still unknown, it is believed that the cappilary permeability is changed in CSF (13,14,19,21).

Nowadays by the optimal combination of antiemetic agents, cisplatin induced emesis can be controlled in 60-80% (2-4).

Gralla and his group used high dose metoclopramide and managed to control emesis in 20-38%. However the combination of metoclopramide-corticosteroid could control emesis in 73%. In the above mentioned study; the complete response was 76% and maximal response 92%. In the second day 78% and 92% responses were obtained respectively (5). In another study; metoclopramide-dexamethasone-lorazepam were used by Kris et al and the emetic control was achieved in acute emesis (85%) and delayed emesis (52%) (21).

Ondansetron is more effective with respect to metoclopramide in the control of emesis induced by cisplatin. The studies indicate that when ondansetron is used alone the emetic control is lower than the optimal (25-35%) (4,7,11,12). 60-73% emetic control has been achieved by using ondansetron while 41-51% control has been achieved by using metoclopramide (2,9,11).

Howthorn et al proved that suboptimal effect of ondansetron could be increased by using dexamethasone in the animal and human experiments. The same result was also reported by Smith et al (8). The combined usage of ondansetron with dexamethasone controls emesis more effectively (Ondansetron-dexamethasone controled emesis 89%, while ondansetron alone could control emesis in 64%) (12,20). There are several other studies which prove this phenomena (1,7).

The responses in the acute emetic control is changed in the delayed emesis. Metoclopramide-dexamethasone treatment was more valuable in controlling the delayed emesis (6,19). Smith et al has reported that they could control delayed emesis (78%) by using oral metoclopramide-dexamethasone as an antiemetic agent in the first 5 days (8).

Harmsworth and his friends used ondansetran not only in single day treatment but in consequitive days of cisplatin treatments and managed an emetic control in 65-93%. However they pointed out that the best results were obtained in the first two days and in the 3^-4^ days the emetic control decreased (3-9). This data remarks that; different mechanisms take place in the delayed emesis.

Ondansetron could achieve the emetic control (80-90%) with the patients having antiemetic resistance (4).

In our study we used; ondansetron-dexamethasone and metoclopramide-dexamethasone and our results are suitable with the literature. The acute emesis was completely controlled with ondansetron-dexamethasone in 45.5% and with metoclopramide-dexamethasone in 26.5% also, major responses were 81.9% and 61.3% respectively.

However in the control of delayed emesis a significant difference between drugs could not be obtained. In delayed emesis; emetic control was about 84-86% for both groups.

Distonic reactions were not observed in the metoclopramide group but young patients had extrapramidal symptoms (10,13,18,19). In the ondansetron group these symptoms were not observed but, elavation of serum transaminase level (2,20) (9 patients had elevated serum transaminase level).

Finally; it can be concluded that ondansetron-dexamethasone is more effective in the control of acute emesis but further studies are required for the delayed emetic contro.

Sisplatin içeren kemoterapi protokollerinde metoklopramid Me ondansetronun antiemetik etkilerinin karşılaştırılması

Sisplatinle oluşan emezisin kontrolünde ondansetron (5 hidroksitriptamin reseptör antagonist!) He deksametazon kombinasyonu, metoklopramid-deksametazon kombinasyonu ile karşılaştırıldı. Akciğer kanseri tanısı alan 88 hastaya farklı protokollerde 80 mgjm²/gün dozda sisplatin verildi. 44 hastaya undans^.. <n-deksametazon, 44 hastaya

metoklopramid-deksametazondan oluşan anti-emetik tedavi uygulandı. Akut emeziste (ilk 24 saat) ondansetron grubunda %45.5, metoklopramid grubunda %29.5 tam kontrol sağlandı (p<0.05). Tam ve maksimal yanıt ondansetron grubunda %81.9, metoklopramidgrubunda %61.3 oldu (p<0.01). Akut emezis kontrolünde ondansetron grubunun istatistiksel olarak anlamlı üstünlüğü görüldü. Ancak geç emezis kontrolünde iki grup arasında anlamlı farklılık olmadı. Hastalar her iki antiemetik tedaviyi iyi tolere ettiler. Geç emezis kontrolünde ondansetronun rolünü değerlendirmek için daha geniş çalışmalar gerekmektedir.
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