Original article
UDC: 616-006:616-01/-09:615-085



# Antiemetics: Side effects and reactions

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**BACKGROUND:** *The purpose of this study was to evaluate the side effects and reactions caused by different antiemetics reported by patients who were receiving high emetogenic, cisplatin (CIS) containing and moderately emetogenic, Cyclophosphamide (CY) containing chemotherapy.*

**METHODS:** *A total of 260 cancer and lymphoma patients were studied. High dose metoclopramide (MCL), ondansetron (OND), granisetron (GRA) and tropisetron (TRO) alone or in combination with corticosteroids were used for the control of emesis. Side effects and reactions were evaluated according to data, reported in "patient diary" on day 1-6.*

**RESULTS:** *A total of 11.2% patients, receiving CIS - containing chemotherapy and 8.2% - CY containing chemotherapy reported side effects. The most serious side effect was headache ranged from 11.4% in the OND group to 7.1% in GRA group. The other side effects and reaction were constipation, diarrhea, extrapyramidal reactions.*

**CONCLUSION:** *MCL and setrons, alone or in combination with CS, were well tolerated. The most frequent side effects observed with dose MCL were extrapyramidal reactions and with setrons - headache and constipation.*

**KEY WORDS:** *Antiemetics+adverse effects; Metoclopramide; Antineoplastic Agents+adverse effects; Serotonin Antagonists*

*Archive of Oncology 2001,9(3):151-153©2001,Institute of Oncology Sremska Kamenica, Yugoslavia*

## INTRODUCTION

The antiemetics take very important place in the treatment of cancer patients, treated with chemo- and radiotherapy. As well as anticancer drugs they have side effects and reactions. The "ideal antiemetic" must respond to the following criteria: to provide complete antiemetic control, lack of side effects, simple and easy application, and acceptable price. At the present time the clinical practice uses most often 5-$HT_3$ receptor antagonists, well known as setrons and metoclopramide (MCL), both alone or in combination with corticosteroids (CS).

The frequency of the side effects varies between 5-15%. In the high doses MCL the most common side effects are extrapyramidal reactions, especially in the young patients. Constipation, diarrhea, headache are observed more rarely and their frequency depends on the used dose and duration of the treatment. The prolonged application of the corticosteroids provokes hyperglicemia, fluid retention, stomach irritation etc. (1,2).

The setrons show similar side effects. The headache is observed in about 10-15%, constipation in 3-10%, diarrhea - 1% and the others reactions - supersensitivity, hepatotoxicity are rare (3,4,5). Seldom, the setrons cause dose-dependant changes in the ECG (QT-interval) or in the cardiac rhythm (6).

The aim of this study was to evaluate the side effects and reactions of metoclopramide (MCL) and setrons - ondansetron (OND), granisetron (GRA), tropisetron (TRO).

## MATERIALS AND METHODS

### Patients and chemotherapy

The study was performed according to the standards of the ethical committee. Patients were eligible for this study provided they were at last 18 years of age, had histologically confirmed cancer

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The manuscript was received: 19. 07. 2001.

Provisionally accepted: 24. 09. 2001.

Accepted for publication: 25. 09. 2001.

or lymphoma and had a WHO performance status score of 2 or less. Patients were excluded if they had marked hepatic dysfunction, hypercalcemia, congestive heart failure, active peptic ulcer, brain tumors or central nervous system metastases and gastrointestinal (MALT) lymphoma. Patient characteristics are shown in Table 1.

**Table 1.** Patient characteristics

| Characteristics | Number of patients (%) |
|---|---|
| Total | 260 |
| males | 182 (70.0%) |
| females | 78 (30.0%) |
| Median age (yrs) | 44.9 SD 14.4 (18-70) |
| Median B.S.A. ($m^2$) | 1.92 SD 0.11 (1.62-2.18) |
| Primary tumor site | |
| lung | 89 (34.2%) |
| testis | 46 (17.7%) |
| ovary | 24 (9.2%) |
| breast | 41 (15.8%) |
| Hodgkin's lymphoma | 46 (17.7%) |
| non-Hodgkin's lymphoma | 14 (5.4%) |

The treatment was carried out according to the standard protocols. Hundred and fifty-nine (61.1%) patients received high emetogenic, cisplatin (CIS)-containing and 101(38.9%) patients - moderately emetogenic Cyclophosphamide (CY)-containing chemotherapy (CHTH). First group received at least 50 mg/$m^2$ of CIS and the second - at least 500 mg/$m^2$ CY. The most used cytotoxic agents are shown in Table 2.

**Table 2.** Applied cytotoxic agents

| Agent | Number of patients (%) |
|---|---|
| Cisplatin | 159 (61.1%) |
| Cyclophosphamide | 132 (50.8%) |
| Doxorubicin / Epirubicin | 57 (21.9%) / 72 (27.7%) |
| Mechlorethamine | 7 (2.7%) |
| Bleomycin | 72 (27.7%) |
| Vincristine /Vinblastine | 34 (13.1%) / 72 (27.7%) |
| Etoposide | 25 (9.6%) |
| Mitoxantrone | 20 (7.7%) |
| Dacarbazine | 26 (10.0%) |

### Antiemetic therapy

On day 1 patients with CIS - containing CHTH received MCL 2 mg/kg or OND 24 mg for prevention of acute emesis, both as total daily dose (tdd), given in 3 divided doses IV over 15 min. GRA was infused 3 mg IV and TRO - 5 mg IV as a single daily dose. The same doses of setrons were given orally on days 2-6 for delayed emesis. In this phase, MCL was given orally 1 mg/kg t.i.d. A total of 310 cycles CHTH were evaluated.

Patients with CY - containing CHTH received MCL 1 mg/kg or OND 24 mg alone or in combination with dexamethasone (DEX) 8 mg/$m^2$ tdd on day 1 for acute emesis (as above). During delayed phase, patients received MCL 0.5 mg/kg and OND - 24 mg tdd, given orally in 3 divided doses. DEX was used in dose 8 mg/$m^2$ orally (as above). Some patients received equivalent doses of methylprednisolone and prednisolone in acute and delayed phase. A total of 292 cycles were evaluated.

All side effects and reactions in acute and delayed emesis were reported by patients in "patient diary" and investigated over repeated cycles of chemotherapy.

All calculations were performed by SPSS/PC - v. 5.02 statistical computing package.

## RESULTS

A total of 260 patients (median age 44.9 years, range from 18 to 70 years) were enrolled in the study.

**High emetogenic (CIS) - containing chemotherapy:** A total of 310 cycles were evaluated: 130 patients were treated with setrons (OND, GRA, TRO) and 180 received MCL. The most commonly reported side effects and reactions are shown in Table 3.

**Table 3.** Side effects and reaction in CIS-containing chemotherapy

| | Antiemetic therapy (evaluated cycles) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | MCL (n=180) | | OND (n=70) | | | GRA (n=28) | | | TRO (n=32) | | | Total (n=310) | |
| Side effects and reaction | No | % | No | % | p value | No | % | p value | No | % | p value | No | % |
| Headache | 4 | 2.2 | 8 | 11.4 | NS | 2 | 7.1 | NS | 3 | 9.4 | NS | 17 | 5.5 |
| Constipation | - | | 6 | 8.6 | p<0.001 | 1 | 3.6 | NS | 2 | 6.2 | NS | 9 | 2.9 |
| Diarrhea | 1 | 0.6 | 1 | 1.4 | NS | | - | | | - | | 2 | 0.6 |
| Extrapyramidal reaction | 6 | 3.3 | | - | | | - | | | - | | 6 | 1.9 |
| Supersensitivity | 1 | 0.6 | | - | | | - | | | - | | 1 | 0.3 |
| Total | 12 | 6.7 | 15 | 21.4 | NS | 3 | 10.7 | NS | 5 | 15.6 | NS | 35 | 11.2 |

NS: not significant

A total of 11.2% patients reported side effects and reactions. The most frequent side effect was headache - in 5.5%, followed by obstipation - 2.9% and extrapyramidal reactions - in 1.9%. The last were observed only in the patients, treated with MCL. Diarrhea and supersensitivity were observed in <1%.

Depending on the different antiemetic treatments, side effects were found in 6.7% patients receiving MCL, 21.4% - OND, 10.7% - GRA and 15.6 % - TRO (p>0.10). Headache was ranged from 2.2% in MCL group to 11.4% in OND group. Constipation was observed in 8.6% patients, receiving OND, 3.6% GRA and 6.2%-TRO. No one patient reported constipation in the MCL group and it was observed significantly more often in the OND group.

Extrapyramidal reactions were observed only in the patients, receiving MCL - 3.3%. They were mild in four patients, and two patients had severe reactions imposing additional treatment with benzodiazepines and antihistamines. Headache was reported in 2.2% of the patients, receiving MCL and <1% had diarrhea and supersensitivity to the drug. They were mild and influenced by conventional therapy. There were no significant differences in the side effects observed in the evaluated antiemetics.

**Moderately emetogenic (CY) - containing chemotherapy:**

A total of 292 cycles were evaluated: 82 patients, treated with OND±CS and 210 - MCL±CS. The results are shown in Table 4.

A total of 8.2% patients reported side effects and reactions: headache was observed in 4.1%, constipation - in 3.4% and diarrhea - in 0.7%. In OND±CS group headache was reported by

8.5%, constipation - 7.3% and diarrhea - 1.2% patients. They were also mild and rapidly controlled with symptomatic therapy. In the MCL±CS group, headache was reported by 2.4%, constipation - 1.9% and diarrhea - 0.5% patients. There were no significant differences in the side effects observed in the evaluated antiemetics.

**Table 4.** Side effects and reaction in CY-containing chemotherapy

| Side effects and reaction | Antiemetic therapy (evaluated cycles) OND ± CS (n=82) No | % | MCL ± CS (n=210) No | % | p value | Total (n=292) No | % | p value |
|---|---|---|---|---|---|---|---|---|
| Headache | 7 | 8.5 | 5 | 2.4 | NS | 12 | 4.1 | NS |
| Constipation | 6 | 7.3 | 4 | 1.9 | NS | 10 | 3.4 | NS |
| Diarrhea | 1 | 1.2 | 1 | 0.5 | NS | 2 | 0.7 | NS |
| Extrapyramidal reaction | - | | - | | | - | | |
| Supersensitivity | - | | - | | | - | | |
| Total | 14 | 17.1 | 10 | 4.8 | NS | 24 | 8.2 | NS |

NS: not significant

## DISCUSSION

Antiemetic therapy is usually well tolerated. Setrons have the same profile of side effects with this observed in MCL - well known. Most of the studies discuss the side effects of the antiemetics along with the evaluation of their efficacy. In the delayed emesis, Kandemir EG et al. (7) reported 30.4% constipation in patients, received OND plus DEX, compared with 9.3% - treated with MCL plus DEX ($p<0.01$). No significant differences were observed in patients with headache - 15.2% in OND plus DEX group vs. 13.9% in MCL plus DEX group. Dizziness was reported by 6.5% in the first group and in 9.3% in the second group. Diarrhea was observed in 13.0% and 9.3% respectively.

In Bulgaria, Tzekova VI et al. (8) reported side effects in 16% patients, treated with GRA. There were mainly headache and dizziness. Summarizing their experience with GRA in other study, they observed headache in 16%, dizziness in 14% and hypotension in 2% of the patients (9). The other authors reported headache in about 10-15 %, diarrhea - up to 1% and the other side effects and reactions such as supersensitivity and liver dysfunction were very rare (3,10).

In the present study the most expressive headache was observed with setrons, achieving to 11.4% of the patients, in OND group received CIS-containing chemotherapy. Second important side effect was obstipation, ranged between 8.6% for OND to 3.6% in GRA. The side effects, more frequently headache and obstipation, in patients who received moderately emetogenic chemotherapy, were in the same ranges.

## CONCLUSION

In conclusion, MCL and setrons used alone or in combination with corticosteroids are well tolerated. This study showed that the different chemotherapies did not influence the frequency of the side effects and reactions, caused by used antiemetic drugs. The most common side effects were extrapyramidal reactions in the high dose MCL and in setrons - headache and constipation. They are usually mild and controlled by symptomatic treatment, but they have to be identified by the medical staff and the patients.

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