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# ONDANSETRON VERSUS METOCLOPRAMIDE AS ANTIEMETIC TREATMENT DURING CISPLATIN-BASED CHEMOTHERAPY

## A prospective study with special regard to electrolyte imbalance

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**Cancer patients selected for cisplatin-based chemotherapy were randomly divided into two groups (42 patients in each) which received either metoclopramide or ondansetron as antiemetics. Metoclopramide was given i.v. with 5 doses of 2 mg/kg starting 30 min before the cisplatin infusion and continued with one dose every 3 h. Ondansetron was given with a first injection of 8 mg i.v. 30 min before the cisplatin infusion; the patients were given 8 mg orally 5 and 10 h after the cisplatin infusion followed by 8 mg × 3 during the next two days. In the present study ondansetron was superior to metoclopramide concerning antiemetic efficacy and gave also less side-effects as diarrhea, dizziness, extrapyramidal symptoms and electrolyte imbalance (sodium, potassium, magnesum, phosphorous) during the first 24 h following the cisplatin infusion.**

Until recently metoclopramide was the most commonly used antiemetic drug in patients receiving cisplatin-based chemotherapy. The antiemetic efficacy of high-dose metoclopramide was demonstrated in our previously reported studies (1–4).

A new group of antiemetic drugs are specific antagonists of 5-hydroxytryptamine (5-HT) at the 5-HT receptor and ondansetron belongs to this category. These drugs are considered highly effective in controlling emesis induced by cytostatic chemotherapy and have been reported to be superior to metoclopramide in treatment of acute emesis (5–7).

We compared in the present study the efficacy of ondansetron and metoclopramide in cancer patients receiving cisplatin-based chemotherapy and also side-effects, including electrolyte disturbances which may accompany the chemotherapy.

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### Material and Methods

Eighty-four patients with histologically confirmed cancer were entered into this prospective randomized study. Only patients < 70 years old, not previously given chemotherapy and with a Karnofsky index of > 60% were included. All patients received cisplatin-based combination chemotherapy. As required for the concurrent chemotherapy protocols, each patient had a leukocyte count of $> 4.10^9$/l, a platelets count above $> 100.10^9$/l, serum creatinine below 14 mg/l, and serum bilirubin below 10 mg/l (Table 1).

Pretreatment evaluation included history and physical examination, blood cell counts, biochemical profile, serum electrolytes and creatinine clearance, electrocardiogram and chest roentgenogram. Follow-up biochemical and hematologic tests were performed twice a week during the first week of treatment and weekly thereafter; chest roentgenogram and creatinine clearance were obtained monthly.

The distribution of age, sex, Karnofsky index and site of primary cancer were fairly similar in the two groups (Table 1).

All patients were hospitalized to receive cisplatin at a dose of 100 mg/m$^2$ area in 30 min i.v. infusion after hydration with mannitol. Patients with non-small cell lung cancer

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**Table 1**

*Patients clinical characteristics. The median age (range) was in group A 56 (36–70) years and in group B 57 (22–70) years. None of the patients had previously received cancer chemotherapy and antiemetic therapy*

| Characteristics | Group A Metoclopramide n | Group B Ondansetron n |
|---|---|---|
| Number of patients | 42 | 42 |
| Sex | | |
| Males | 28 | 33 |
| Females | 14 | 9 |
| Karnofsky index | | |
| 90–100 | 13 | 21 |
| 80 | 18 | 14 |
| 70 | 11 | 7 |
| Type of cancer | | |
| Lung | 25 | 17 |
| Ovarian | 1 | 2 |
| Head & neck | 5 | 6 |
| Other | 11 | 17 |

also received vinblastine (6 mg/m$^2$). Patients with ovarian cancer also received cyclophosphamide, with head and neck cancer 5-fluorouracil, with mesothelioma vinblastine and with testicular cancer etoposide and bleomycin.

The antiemetic drugs were administered as follows:

Group A (42 patients): Metoclopramide was given i.v. with 2 mg/kg every 2 h in 5 injections, the first given 30 min prior to cisplatin. The metoclopramide was diluted in 50 ml of 0.9% sodium chloride and infused in 15 min.

Group B (42 patients): Ondansetron was given with 8 mg in 100 ml N/S as 15 min i.v. infusion just before the infusion of cisplatin, followed by 8 mg orally in the afternoon (5 h after the first dose) and at night (10 h after the first dose). The next two days the patients were given 8 mg odansentron × 3 orally.

The electrolytes sodium, potassium, calcium, phosphorous, and magnesium were determined before and 24 h after the infusion of cisplatin. The patients received the particular antiemetic treatment only during their first course of chemotherapy.

Nausea and vomiting were evaluated by the medical personnel 24 h after cisplatin infusion by interviewing the patients. We registered the number of vomiting attacks with and without gastric content (retches) and the duration of nausea on a bedside record form. Monitoring was accomplished through direct observation and patient interviews.

Vomiting was graded according to Gralla (8); complete response (no emetic episodes), major response (1–2 emetic episodes) minor response (3–5 emetic episodes) or failure ( > 5 emetic episodes or reduce antiemetic therapy required within 24 h). One emetic episode was defined as any episode of vomiting with or without gastric content (retching).

Side-effects of the treatment were also directly observed and recorded. Activity during the trial was graded as follows: 0 (normal activity), 1 (mild impairment of activity), and 2 (moderate to severe impairment of activity). The influence on the patient's appetite was graded as follows: 0 (appetite similar or better than usual), 1 (less than usual, some solids), 2 (liquid only), 3 (nothing by mouth). Any sedative effect was evaluated as follows: 0 (none), 1 (mild, patient lethargic but wakened by verbal stimuli and completely oriented to time, place, and person when awake), 2 (moderate, patient wakened only by physical stimuli but completely oriented when awake), and 3 (marked, patient wakened only by physical stimuli and disoriented when awake). Diarrhea during the trial was graded as follows: 0 (none), 1 ( < 3 episodes), 2 (3–6 episodes), 3 ( > 6 episodes, intolerable and requiring therapy).

Patients were assessed for side-effects of the antiemetics, such as chills, diaphoresis, diarrhea, headache, dizziness, hypotensive symptoms, ataxia, hallucination, euphoria, extrapyramidal manifestation, or other symptoms. Patients were awakened if necessary and side-effects assessed before each dose of antiemetic medication, at the end of the 24-h observation period, and at least every 3 h during the trial.

For statistical analysis ondansetron and metoclopramide were compared with regard to number of emetic episodes using the Wilcoxon rank-test (9). Categorical variables were compared by means of the $\chi^2$-test, with Yales correction when appropriate; continuous variables were compared by Student's t-test or a non-parametric test (Mann-Whitney's) for two group comparisons, and Student's t-test or Wilcoxon's signed rank-test, when appropriate, for matched pairs, after logarithmic transformation when needed to correct the distribution (10). Multiple linear regression analysis was performed to correlate the level of different electrolyte values.

## Results

As seen in Table 2 the mean number of vomiting attacks the gastric content was significantly higher in group A than in group B ($p < 0.006$). Control of vomiting grade 3 was also better in group B than in group A ($p < 0.023$). The mean duration of nausea was shorter in group B than in group A with borderline significance ($p = 0.052$). The mean number of vomiting attacks without gastric content was also lower in group B but this difference was not statistically significant ($p = 0.1$).

Regarding toxicity, diarrhea ($p < 0.0001$), reduction of activity ($p < 0.06$) and loss of appetite ($p < 0.1$) were more pronounced in group A. The sedative effect was about the same in the two groups (Table 3). Concerning other parameters of toxicity (Table 4), no extrapyramidal manifestations were noticed in group B ($p < 0.046$) and dizziness was also less pronounced in this group ($p < 0.016$).

**Table 2**

*Mean number of vomiting attacks with or without gastric content (± SD), mean duration of nausea (± SD), and clissification according to control of vomiting during the first 24 h*

| | Group A Metoclopramide | Group B Ondansetron | p-value |
|---|---|---|---|
| Mean number of vomiting attacks with gastric cancer content | 3.02 ± 3.65 | 1.23 ± 1.89 | 0.006 |
| Mean number of vomiting attacks without gastric content | 5.40 ± 7.44 | 3.51 ± 3.98 | 0.163 |
| Mean duration of nausea (min) | 174 ± 198 | 101 ± 135 | 0.052 |
| Control of vomiting | | | |
| Grade 0 | 11 pts | 11 pts | – |
| Grade 1 | 11 pts | 19 pts | 0.1 |
| Grade 2 | 8 pts | 9 pts | – |
| Grade 3 | 12 pts | 3 pts | 0.023 |

**Table 3**

*Numbers of patients with different grades of toxicity during the first 24 h*

| Side-effects | Grade | Group A Metoclopramide | Group B Ondansetron | p-value |
|---|---|---|---|---|
| Sedative effects | 0 | 36 | 39 | – |
| | 1 | 6 | 2 | – |
| | 2 | 1 | 1 | – |
| Loss of appetite | 0 | 12 | 11 | – |
| | 1 | 5 | 14 | 0.1 |
| | 2 | 11 | 12 | – |
| | 3 | 14 | 5 | 0.1 |
| Reduction of activity | 0 | 17 | 14 | – |
| | 1 | 10 | 23 | 0.06 |
| | 2 | 15 | 5 | 0.06 |
| Diarrhea | 0 | 22 | 41 | 0.0001 |
| | 1 | 2 | 1 | – |
| | 2 | 11 | 0 | 0.005 |
| | 3 | 7 | 0 | 0.032 |

**Table 4**

*Number of patients with some parameters of toxicity during the first 24 h (only constipation was estimated during three days)*

| Side-effects | Group A Metoclopramide | Group B Ondansetron | p-value |
|---|---|---|---|
| Chills | 3 | 3 | – |
| Diaphoresis-hallucination | 17 | 8 | – |
| Headache | 9 | 13 | 0.1 |
| Dizziness | 6 | 0 | 0.016 |
| Hypotensive symptoms | 4 | 1 | – |
| Extrapyramidal manifestations | 3 | 0 | 0.046 |
| Mouth dryness | 14 | 12 | – |
| Constipation (in 3 days analysis) | 0 | 15 | 0.0001 |

**Table 5**

*Mean value and mean differences ( ± SD) of the examined serum electrolytes before and 24 h after the infusion of cisplatin. The values are given as mEq./100 ml*

| Serum electrolytes | Group A Metoclopramide | | | Group B Ondansetron | | | p-value |
|---|---|---|---|---|---|---|---|
| | Before | After | Diff. | Before | After | Diff. | |
| Na | 139.5 | 134.7 | 4.8 ± 3.2 | 137.9 | 135.2 | 2.8 ± 2.4 | 0.002 |
| K | 4.3 | 3.8 | 0.5 ± 0.3 | 4.4 | 4.1 | 0.3 ± 0.2 | 0.001 |
| Ca | 8.7 | 8.4 | 0.4 ± 0.3 | 9.0 | 8.6 | 0.5 ± 0.4 | 0.16 |
| Mg | 2.0 | 1.5 | 0.5 ± 0.3 | 1.8 | 1.6 | 0.2 ± 0.3 | 0.0001 |
| P | 3.6 | 3.2 | 0.3 ± 0.2 | 3.8 | 3.5 | 0.3 ± 0.2 | 0.9 |

Headache was, however, somewhat more common in group B ($p = 0.1$).

In Table 5 the differences in between electrolyte values measured before infusion of cisplatin and 24 h after are presented. Sodium, potassium, and magnesium decreased significantly less (p-values 0.002–0.0001) in group B than in group A, whereas there were no significant differences between the groups as to change of calcium and phosphorus.

## Discussion

In the present study ondansetron had superior antiemetic efficacy compared to metoclopramide during the first 24 h. The superiority of ondansetron was demonstrated by less vomiting with gastric content, shorter duration of nausea, and better control of vomiting symptoms. Extrapyramidal manifestations were completely absent in the ondansetron group and dizziness, diarrhea, and diaphoresis were less frequent. Only headache seemed more common with the use of ondansetron.

Our results compare well with the results of similar studies (5–7). $H_3$-antagonists are more effective, produce fewer adverse events and are easier to administer than metoclopramide for the prevention of emesis associated with cisplatin chemotherapy.

It is known that cisplatin may induce electrolyte disturbances (11, 12). The reason why we found less electrolyte disturbances in the ondansetron group was probably a decreased number of vomiting attacks with gastric content, diarrhea, and diaphoresis in this group. The differences may also have been influenced by more pronounced reduction of food intake in the metoclopramide group because of more intense nausea and vomiting.

The present study strongly suggests that ondansetron is superior to metoclopramide in control of nausea and vomiting and that it gives fewer side-effects and thereby indirectly less electrolyte disturbances after the administration of cisplatin. However, during the delayed phase the efficacy of the two antiemetic drugs seemed to be equal.

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