# Comparison of the Efficacy and Safety of Tropisetron, Metoclopramide, and Chlorpromazine in the Treatment of Emesis Associated with Far Advanced Cancer

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**BACKGROUND.** A single institution, prospective, randomized trial was performed in terminal cancer patients to compare tropisetron (TRO), metoclopramide (MET), and chlorpromazine (CHL) in the management of nausea and emesis. Patients had far advanced cancer, were far removed from chemotherapy or radiotherapy, and their nausea and emesis was not due to bowel obstruction, drug intake, or cranial, electrolytic, or metabolic causes. The effects of antiemetic treatments were evaluated from Days 1–15.

**METHODS.** Two hundred and eighty patients were randomized to receive 1) MET+ dexamethasone (DEX) (10 mg∗4 and 2 mg∗1, respectively, orally), 2) TRO (5 mg∗1, orally), 3) TRO + MET (5 mg∗1 and 10 mg∗2, respectively, orally), 4) TRO + MET + DEX (5 mg∗1, 10 mg∗2, and 2 mg∗1, respectively, orally), 5) CHL + DEX (25 mg∗2 and 2 mg∗1, respectively, orally), 6) TRO + CHL (5 mg∗1 and 12.5 mg∗2, respectively, orally), or 7) TRO + CHL + DEX (5 mg∗1, 12.5 mg∗2, and 2 mg∗1, respectively, orally). Total control was defined as no nausea or emesis.

**RESULTS.** By the end of the 15th day, total control of emesis was obtained in 23.6% (9 of 38) of MET + DEX patients, 78.9% (30 of 38) of TRO patients, 84.2% (32 of 38) of TRO + MET patients, 92.3% (36 of 39) of TRO + MET + DEX patients, 33.3 (13 of 39) of CHL + DEX patients, 84.6% (33 of 39) of TRO + CHL patients, and 92.5% (37 of 40) of TRO + CHL + DEX patients. Total control of nausea was achieved in 18.4% (7 of 38) of MET + DEX patients, 65.7% (25 of 38) of TRO patients, 73.6% (28 of 38) of TRO + MET patients, 87.1% (34 of 39) of TRO + MET + DEX patients, 17.9% (7 of 39) of CHL + DEX patients, 74.3% (29 of 39) of TRO + CHL patients, and 85% (34 of 40) of TRO + CHL + DEX patients. When comparing MET + DEX versus TRO; MET + DEX versus TRO + MET; MET + DEX versus TRO + MET + DEX; MET + DEX versus TRO + CHL; MET + DEX versus TRO + CHL + DEX; CHL + DEX versus TRO; CHL + DEX versus TRO + MET; CHL + DEX versus TRO + MET + DEX; CHL + DEX versus TRO + CHL; and CHL + DEX versus TRO + CHL + DEX, significant differences were noted. All antiemetic drugs were well tolerated with no severe side effects observed in any treatment arm.

**CONCLUSIONS.** These data suggest that 5-HT3 receptor antagonists such as tropisetron clinically are more effective in the control of emesis of patients with far advanced cancer than previously used agents. This study raises important issues when attempting to decide which antiemetic therapy to choose for an individual patient with far advanced disease. ***Cancer*** **1998;83:1214–23.** © *1998 American Cancer Society.*

**KEYWORDS: emesis, nausea, far advanced cancer, tropisetron, metoclopramide, chlorpromazine.**

Most patients with cancer experience nausea and emesis at some stage during their illness. This symptom complex occurs after

chemotherapy or radiotherapy or as a chronic syndrome in patients with advanced cancer receiving no antineoplastic treatment. Nausea and emesis are nearly universal symptoms of advanced cancer. Reports of its prevalence suggest that nausea occurs in 60% of terminal cancer patients.[1] Emesis is less common, occurring in approximately 30% of patients.[2]

Nausea and emesis are of clinical significance in that they add to the overall adverseness of the terminal cancer stage. For the patient, nausea and emesis not only indicate high levels of stress and anxiety with regard to their condition, but also promote further disturbance because of others' reactions, family and staff avoidance, and patient self-deprecation. Nausea and emesis may directly interfere with life by compromising the patient through nutritional debilitation and metabolic derangement. In addition, patients who reflexively regurgitate oral medication may not be receiving maximal analgesic doses. Nausea and emesis are significant concerns in terminal cancer patients and their optimal management can be critical to the patient's physical and emotional well being. Ideally, all patients with far advanced cancer should have complete control of nausea and emesis.

In patients with far advanced cancer, nausea and emesis may be due to gastrointestinal causes (e.g., gastric stasis or bowel obstruction), cranial causes (e.g., intracranial metastases), electrolytic causes, metabolic causes (e.g., uremia or hypercalcemia), or to drug intake (e.g., opioids).[3]

During the past decade a growing number of antiemetic regimens for use in patients with emesis associated with far advanced cancer have been presented. High dose metoclopramide (MET), corticosteroids, phenothiazines, and benzodiazepines alone or in various combinations currently are the drugs used most frequently.[4–6] Clinically significant side effects (extrapyramidal symptoms and sedation) also have been reported.[7]

Although the advantages of the 5-hydroxytryptamine (5-HT3) receptor antagonists versus traditional antiemetic combination therapy now generally are acknowledged in chemotherapy- or radiotherapy-induced emesis,[8–10] it is of interest to test these drugs in the palliative care setting in patients with emesis far from chemotherapy or radiotherapy. Their current use is restricted to chemotherapy- or radiotherapy-induced nausea and emesis and to postsurgical emesis.[11] However, 5-HT3 receptor antagonists may have a wider role to play.

To our knowledge, to date only one published study has been reported regarding the use of 5-HT3 antagonists in the management of emesis associated with far advanced cancer.[12] The purpose of this study was to evaluate and compare the antiemetic efficacy and tolerability of tropisetron (TRO) with standard antiemetic therapy in the control of nausea and emesis associated with far advanced cancer. The patients studied had experienced insufficient control of emesis with standard (MET- or chlorpromazine [CHL]-containing regimens) antiemetic therapy. Their nausea and emesis was not due to cranial, electrolytic, or metabolic causes, drug intake, chemotherapy, or radiotherapy.

Seven antiemetic regimens were compared: 1) MET plus dexamethasone (MET+DEX), 2) TRO, 3) TRO+MET, 4) TRO+MET+DEX, 5) CHL+DEX, 6) TRO+CHL, and 7) TRO+CHL+DEX.

## METHODS

After obtaining approval from the ethics committee of our institute and written informed consent from the patients, a single institution, prospective, parallel group, randomized study was performed to compare TRO, MET, and CHL in the control of nausea and emesis associated with far advanced cancer. The study was conducted in accordance with the Helsinki Declaration.

### Patients and Study Design

In this study 280 patients who had experienced insufficient emesis control ($>$ 3 episodes within 24 hours) while receiving standard antiemetics took part. More specifically, 140 patients received MET (10 mg*2) and 140 patients received CHL (25 mg*2). Patients receiving MET were assigned randomly (2:2:2:1) to 4 groups: 1) MET+DEX (10 mg*4 and 2 mg*1, respectively, orally), 2) TRO+MET (5 mg*1 and 10 mg*2, respectively, orally), 3) TRO+MET+DEX (5 mg*1, 10 mg*2, and 2 mg*1, respectively, orally), and 4) TRO (5 mg*1). Patients receiving CHL were assigned randomly (2:2:2:1) to 4 groups: 5) CHL+DEX (25 mg*2 and 2 mg*1, respectively, orally), 6) TRO+CHL (5 mg*1 and 12.5*2, respectively, orally), 7) TRO+CHL+DEX (5 mg*1, 12.5 mg*2, and 2 mg*1, respectively, orally), and 8) TRO (5 mg*1). After the initial randomization, Groups 4 and 8 were united and formed one single group of 40 patients receiving TRO, so that finally seven groups comprised of 40 patients each were formed and studied.

No other drugs that might impact on emesis (e.g., hypnotics or anxiolytics) were administered during the study period.

Informed consent was obtained from all patients before randomization. Patient characteristics in the seven treatment groups did not differ with respect to gender, age, performance status, and primary site of cancer. Characteristics of the 280 patients entered into the trial are presented in Table 1.

Patients with far advanced cancer were eligible to

**TABLE 1**
**Patient Characteristics at Entry to the Study**

| Characteristic | Treatment group | | | | | | |
|---|---|---|---|---|---|---|---|
| | MET + DEX (n = 40) | TRO (n = 40) | MET + TRO (n = 40) | MET + TRO + DEX (n = 40) | CHL + DEX (n = 40) | CHL + TRO (n = 40) | CHL + TRO + DEX (n = 40) |
| Age (yrs) | | | | | | | |
| Median | 55 | 56 | 61 | 59 | 57 | 60 | 61 |
| Range | 36–75 | 35–73 | 41–78 | 37–72 | 34–72 | 43–77 | 38–78 |
| Gender | | | | | | | |
| Male | 22 | 24 | 17 | 19 | 19 | 22 | 23 |
| Female | 18 | 16 | 23 | 21 | 21 | 18 | 17 |
| Primary diagnosis | | | | | | | |
| Type of cancer | | | | | | | |
| Colon, rectum | 12 | 13 | 9 | 8 | 11 | 12 | 9 |
| Ovary | 9 | 4 | 8 | 7 | 10 | 6 | 7 |
| Uterus, cervix | 7 | 6 | 8 | 10 | 9 | 7 | 8 |
| Pancreas | 3 | 5 | 2 | 4 | 3 | 3 | 4 |
| Stomach | 4 | 6 | 4 | 3 | 3 | 4 | 5 |
| Abdominal sarcoma | 2 | 1 | 4 | 4 | 2 | 3 | 3 |
| Cholangiocarcinoma | 2 | 4 | 3 | 2 | 1 | 3 | 3 |
| Lung | 1 | 1 | 2 | 2 | 1 | 2 | 1 |

MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL: chlorpromazine.

**TABLE 2**
**Opioid Administration before and during the Study**

| Opioid drugs | Dose | No. of patients |
|---|---|---|
| Dihydrocodeine, oral | 120–240 mg | 38 |
| Morphine, oral | 60–300 mg | 143 |
| SC | 10–90 mg | 20 |
| Epidural | 1.5–12 mg | 57 |
| Intrathecal | 1–5 mg | 22 |

SC: subcutaneously.

enter the study if they had a Karnofsky performance status of $> 50$. All patients were receiving low dose MET (10 mg*2) or CHL (12.5 mg*2) to avoid opioid-induced emesis, and good control was observed for a long period of time (25days) until the patients suddenly started experiencing nausea and emesis. All patients were receiving standard analgesic medication (Table 2), were free of pain, and no change was initiated to their medication prior to the onset of emesis. Patients were considered ineligible if they were receiving phenobarbital, riphambicin, phenylbutazone, chemotherapy, or radiotherapy. Patients with metabolic or electrolytic disturbances and emesis of central etiology also were excluded from the study. All patients were outpatients during the study.

## Methods of Evaluation

To determine the efficacy of antiemetic therapy two parameters were evaluated: nausea and emesis. Both nausea and emesis were recorded by the patients in diary cards. The evaluation of the efficacy of the antiemetic drugs was performed through strict cooperation between patients and physicians.

Emesis was evaluated by counting episodes of vomiting (defined as expulsion of stomach contents) and retching (defined as an effort to vomit without expulsion of stomach contents). A vomiting or retching episode was defined as vomiting or retching that was separated by at least 1 minute of no vomiting or retching. Nausea was evaluated by asking the patients to record on a diary card the duration of the nausea.

Control of emesis was considered total if there were no episodes of vomiting or retching during 24 hours, major if 1 episode occurred, minor if 2 episodes occurred, and no control if $> 3$ episodes occurred during 24 hours. Nausea control was considered total if patients did not experience any nausea within 24 hours, major if patients felt nauseated for $< 4$ hours during 24 hours, minor if patients felt nauseated for $> 4$ hours but $< 8$ hours during 24 hours, and no control if nausea persisted for $> 8$ hours within 24 hours.

Patients also recorded adverse effects: constipation, dizziness, weakness, or extrapyramidal symptoms. A section of the diary allowed patients to relate any other upsetting symptoms.

Patients were monitored for up to 15 days to evaluate not only the efficacy of the drug combinations with regard to total emesis control and time of achievement but also the preservation of the results

**TABLE 3**
**Emesis Control at 24 Hours**

| Emesis control at 24 hours | Treatment group | | | | | | |
|---|---|---|---|---|---|---|---|
| | MET + DEX | TRO | MET + TRO | MET + TRO + DEX | CHL + DEX | CHL + TRO | CHL + TRO + DEX |
| Total control | — | 5% | 7.5% | 15% | — | 2.5% | 17.5% |
| Major control | 30% | 35% | 40% | 70% | 35% | 52.5% | 75% |
| Minor control | 65% | 60% | 52% | 15% | 65% | 45% | 7.5% |
| No control | 5% | — | — | — | — | — | — |

MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL: chlorpromazine.

**TABLE 4**
**Nausea Control at 24 Hours**

| Nausea control at 24 hours | Treatment group | | | | | | |
|---|---|---|---|---|---|---|---|
| | MET + DEX | TRO | MET + TRO | MET + TRO + DEX | CHL + DEX | CHL + TRO | CHL + TRO + DEX |
| Total control | — | 5% | 2.5% | 7.5% | — | 7.5% | 10% |
| Major control | 25% | 25% | 25% | 40% | 25% | 27.5% | 50% |
| Minor control | 70% | 62.5% | 62.5% | 50% | 75% | 60% | 40% |
| No control | 5% | 7.5% | 10% | 2.5% | — | 5% | — |

MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL: chlorpromazine.

in time. The evaluation of emesis, nausea, and the adverse effects took place 24 hours after the commencement of therapy, and on the third, seventh, and fifteenth treatment days. The diary cards were brought by the patients to their clinic visit and at that time were checked for completeness; any questions arising were clarified with the patient.

## RESULTS

### Descriptive Statistics

#### Day 1: Nausea and Emesis

By the end of the first treatment day, total control of emesis was not obtained in any of the MET+DEX patients, in 5% (2 of 40) of the TRO patients, in 7.5% (3 of 40) of the TRO+MET patients, in 15% (6 of 40) of the TRO+MET+DEX patients, in none of the CHL+DEX patients, in 2.5% (1 of 40) of the TRO+CHL patients, and in 17.5% (7 of 40) of the TRO+CHL+DEX patients (Table 3). Total control of nausea was not achieved in any of the MET+DEX patients, in 5% (2 of 40) of the TRO patients, in 2.5% (1 of 40) of the TRO+MET patients, in 7.5% (3 of 40) of the TRO+MET+DEX patients, in none of the CHL+DEX patients, in 7.5% (3 of 40) of the TRO+CHL patients, and in 10% (4 of40) of the TRO+CHL+DEX patients (Table 4).

#### Day 3: Nausea and Emesis

By the end of the third day, total control of emesis was obtained in 5% (2 of 40) of the MET+DEX patients, in 42.5% (17 of 40) of the TRO patients, in 65% (26of 40) of the TRO+MET patients, in 75% (30 of 40) of the TRO+MET+DEX patients, in 7.5% (3 of 40) of the CHL+DEX patients, in 67.5% (27 of 40) of the TRO+CHL patients, and in 77.5% (31 of 40) of the TRO+CHL+DEX patients (Table 5). Total control of nausea was achieved in 10% (4 of 40) of the MET+DEX patients, in 30% (12 of 40) of the TRO patients, in 35% (14 of 40) of the TRO+MET patients, in 55% (22 of 40) of the TRO+MET+DEX patients, in 10% (4 of 40) of the CHL+DEX patients, in 42.5% (17 of 40) of the TRO+CHL patients, and in 60% (24 of 40) of the TRO+CHL+DEX patients (Table 6).

#### Day 7: Nausea and Emesis

By the end of the seventh day, total control of vomiting was obtained in 21.1% (8 of 38) of the MET+DEX patients, in 65.8% (25 of 38) of the TRO patients, in 71.1% (27 of 38) of the TRO+MET patients, in 82.1% (32 of 39) of the TRO+MET+DEX patients, in 28.2% (11 of 39) of the CHL+DEX patients, in 71.8% (28 of 39) of the TRO+CHL patients, and in 87.5% (35 of 40) of the TRO+CHL+DEX patients (Table 7). Total control of nausea was achieved in 15.8% (6 of 38) of the

**TABLE 5**
**Emesis Control at the Third Treatment Day**

| Emesis control-3rd day | Treatment group | | | | | | |
|---|---|---|---|---|---|---|---|
| | MET + DEX | TRO | MET + TRO | MET + TRO + DEX | CHL + DEX | CHL + TRO | CHL + TRO + DEX |
| Total control | 5% | 42.5% | 65% | 75% | 7.5% | 67.5% | 77.5% |
| Major control | 50% | 52.5% | 30% | 22.5% | 57.5% | 30% | 20% |
| Minor control | 40% | 5% | 5% | 2.5% | 35% | 2.5% | 2.5% |
| No control | 5% | — | — | — | — | — | — |

MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL: chlorpromazine.

**TABLE 6**
**Nausea Control at the Third Treatment Day**

| Nausea control-3rd day | Treatment group | | | | | | |
|---|---|---|---|---|---|---|---|
| | MET + DEX | TRO | MET + TRO | MET + TRO + DEX | CHL + DEX | CHL + TRO | CHL + TRO + DEX |
| Total control | 10% | 30% | 35% | 55% | 10% | 42.5% | 60% |
| Major control | 60% | 62.5% | 60% | 42.5% | 65% | 55% | 37.5% |
| Minor control | 25% | 7.5% | 5% | 2.5% | 25% | 2.5% | 2.5% |
| No control | 5% | — | — | — | — | — | — |

MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL: chlorpromazine.

**TABLE 7**
**Emesis Control at the Seventh Day**

| Emesis control-7th day | Treatment group | | | | | | |
|---|---|---|---|---|---|---|---|
| | MET + DEX | TRO | MET + TRO | MET + TRO + DEX | CHL + DEX | CHL + TRO | CHL + TRO + DEX |
| Total control | 21.1% | 65.8% | 71.1% | 82.1% | 28.2% | 71.8% | 87.5% |
| Major control | 78.9% | 34.2% | 28.9% | 17.9% | 71.8% | 28.2% | 12.5% |
| Minor control | — | — | — | — | — | — | — |
| No control | — | — | — | — | — | — | — |

MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL: chlorpromazine.

MET+DEX patients, in 47.4% (18 of 38) of the TRO patients, in 52.6% (20 of 38) of the TRO+MET patients, in 71.8% (28 of 39) of the TRO+MET+DEX patients, in 17.9% (7 of 39) of the CHL+DEX patients, in 56.4% (22 of 39) of the TRO+CHL patients, and in 72.5% (29 of 40) of the TRO+CHL+DEX patients (Table 8).

### Day 15: Nausea and Emesis

By the end of the fifteenth day, total control of vomiting was obtained in 23.7% (9 of 38) of the MET+DEX patients, in 78.9% (30 of 38) of the TRO patients, in 84.2% (32 of 38) of the TRO+MET patients, in 92.3% (36 of 39) of the TRO+MET+DEX patients, in 33.3% (13 of 39) of the CHL+DEX patients, in 84.6% (33 of 39) of the TRO+CHL patients, and in 92.5% (37 of 40) of the TRO+CHL+DEX patients (Table 9). Total control of nausea was achieved in 18.4% (7 of 38) of the MET+DEX patients, in 65.8% (25 of 38) of the TRO patients, in 73.7% (28 of 38) of the TRO+MET patients, in 87.2% (34 of 39) of the TRO+MET+DEX patients, in 17.9% (7 of 39) of the CHL+DEX patients, in 74.4% (29 of 39) of the TRO+CHL patients, and in 85% (34 of 40) of the TRO+CHL+DEX patients (Table 10).

### Inferential Statistics

### Between Groups Comparisons

Cross-tabulations between the types of treatment and the response categories were used to evaluate the dif-

**TABLE 8**
**Nausea Control at the Seventh Day**

| Nausea control-7th day | Treatment group | | | | | | |
|---|---|---|---|---|---|---|---|
| | MET + DEX | TRO | MET + TRO | MET + TRO + DEX | CHL + DEX | CHL + TRO | CHL + TRO + DEX |
| Total control | 15.8% | 47.4% | 52.6% | 71.8% | 17.9% | 56.4% | 72.5% |
| Major control | 68.4% | 52.6% | 47.4% | 28.2% | 66.7% | 43.6% | 25% |
| Minor control | 15.8% | — | — | — | 15.4% | — | 2.5% |
| No control | — | — | — | — | — | — | — |

MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL: chlorpromazine.

**TABLE 9**
**Emesis Control at the Fifteenth Day**

| Emesis control-15th day | Treatment group | | | | | | |
|---|---|---|---|---|---|---|---|
| | MET + DEX | TRO | MET + TRO | MET + TRO + DEX | CHL + DEX | CHL + TRO | CHL + TRO + DEX |
| Total control | 23.7% | 78.9% | 84.2% | 92.3% | 33.3% | 84.6% | 92.5% |
| Major control | 76.3% | 21.1% | 15.8% | 7.7% | 66.7% | 15.4% | 7.5% |
| Minor control | — | — | — | — | — | — | — |
| No control | — | — | — | — | — | — | — |

MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL: chlorpromazine.

**TABLE 10**
**Nausea Control at the Fifteenth Day**

| Nausea control-15th day | Treatment group | | | | | | |
|---|---|---|---|---|---|---|---|
| | MET + DEX | TRO | MET + TRO | MET + TRO + DEX | CHL + DEX | CHL + TRO | CHL + TRO + DEX |
| Total control | 18.4% | 65.8% | 73.7% | 87.2% | 17.9% | 74.4% | 85% |
| Major control | 71.1% | 34.2% | 26.3% | 12.8% | 76.9% | 25.6% | 12.5% |
| Minor control | 10.5% | — | — | — | 5.1% | — | 2.5% |
| No control | — | — | — | — | — | — | — |

MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL: chlorpromazine.

ferences, if any, between the different treatment regimen in the Day 1, Day 3, Day 7, and Day 15 periods. The standard Pearson chi-square was the statistic used to assess overall statistical significance and the residual frequencies (i.e., observed minus expected) were used to assess the magnitude of the differences observed ($P = 0.00000$).

To further assess the statistical significance between individual types of treatment, an overall Kruskal-Wallis analysis of variance was performed ($P < 0.005$ ). Individual comparisons were performed using the Mann-Whitney $U$ test (Tables 11 and 12).

### Comparisons within Groups

Cross-tabulations between the types of treatment and the response categories were used to evaluate the differences, if any, between the different treatment regimens on Days 1, 3, 7, and 15. The standard Pearson chi-square was the statistic used to assess overall statistical significance and the residual frequencies (i.e., observed minus expected) were used to assess the magnitude of the differences observed ($P = 0.00000$).

For the assessment of statistical significance within each treatment group, over the entire evaluation period, the Friedman analysis of variance was performed ($P < 0.00000$). Individual comparisons were performed employing the Wilcoxon matched pairs test (Table 13). Patients with minor emesis control withdrew from the study after the third treatment day. The number of patients withdrawing was similar among the groups. More specifically only two patients each withdrew from the MET+DEX, MET+TRO, and

**TABLE 11**
***P* Values (Calculated Using the Mann–Whitney *U* Test) of Individual Comparisons between Groups with Total Emesis Control versus Time**

| | *P* values | | | |
|---|---|---|---|---|
| **Treatment group** | **24 hours** | **3 days** | **7 days** | **15 days** |
| MET + DEX/MET + TRO | NS | 0.000 | 0.000 | 0.000 |
| MET + DEX/MET + DEX + TRO | 0.000 | 0.000 | 0.000 | 0.000 |
| MET + DEX/CHL + DEX | NS | NS | NS | NS |
| MET + DEX/CHL + TRO | NS | 0.000 | 0.000 | 0.000 |
| MET + DEX/CHL + TRO + DEX | 0.000 | 0.000 | 0.000 | 0.000 |
| MET + DEX/TRO | NS | 0.000 | 0.000 | 0.000 |
| MET + TRO/MET + TRO + DEX | 0.002 | NS | NS | NS |
| MET + TRO/CHL + DEX | NS | 0.000 | 0.001 | 0.000 |
| MET + TRO/CHL + TRO | NS | NS | NS | NS |
| MET + TRO/MET + TRO + DEX | 0.000 | NS | NS | NS |
| MET + TRO/TRO | NS | NS | NS | NS |
| MET + TRO + DEX/CHL + DEX | 0.000 | 0.000 | 0.000 | 0.000 |
| MET + TRO + DEX/CHL + TRO | NS | NS | NS | NS |
| MET + TRO + DEX/CHL + TRO + DEX | NS | NS | NS | NS |
| MET + TRO + DEX/TRO | 0.000 | NS | NS | NS |
| CHL + DEX/CHL + TRO | NS | 0.000 | 0.000 | 0.000 |
| CHL + DEX/CHL + TRO + DEX | 0.000 | 0.000 | 0.000 | 0.000 |
| CHL + DEX/TRO | NS | 0.000 | 0.004 | 0.000 |
| CHL + TRO/CHL + TRO + DEX | 0.000 | NS | NS | NS |
| CHL + TRO/TRO | NS | NS | NS | NS |
| CHL + TRO + DEX/TRO | 0.000 | 0.007 | NS | NS |

MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL: chlorpromazine; NS: not significant.

**TABLE 12**
***P* Values (Calculated Using the Mann–Whitney *U* Test) of Individual Comparisons between Groups with Total Nausea Control versus Time**

| | *P* values | | | |
|---|---|---|---|---|
| **Treatment group** | **24 hours** | **3 days** | **7 days** | **15 days** |
| MET + DEX/MET + TRO | NS | 0.001 | 0.000 | 0.000 |
| MET + DEX/MET + DEX + TRO | NS | 0.000 | 0.000 | 0.000 |
| MET + DEX/CHL + DEX | NS | NS | NS | NS |
| MET + DEX/CHL + TRO | NS | 0.000 | 0.000 | 0.000 |
| MET + DEX/CHL + TRO + DEX | 0.002 | 0.000 | 0.000 | 0.000 |
| MET + DEX/TRO | NS | NS | 0.002 | 0.002 |
| MET + TRO/MET + TRO + DEX | NS | NS | NS | NS |
| MET + TRO/CHL + DEX | NS | 0.004 | 0.001 | 0.001 |
| MET + TRO/CHL + TRO | NS | NS | NS | NS |
| MET + TRO/MET + TRO · DEX | 0.003 | NS | NS | NS |
| MET + TRO/TRO | NS | NS | NS | NS |
| MET + TRO + DEX/CHL + DEX | NS | 0.000 | 0.000 | 0.000 |
| MET + TRO + DEX/CHL + TRO | NS | NS | NS | NS |
| MET + TRO + DEX/CHL + TRO + DEX | NS | NS | NS | NS |
| MET + TRO + DEX/TRO | NS | NS | NS | NS |
| CHL + DEX/CHL + TRO | NS | 0.000 | 0.000 | 0.000 |
| CHL + DEX/CHL + TRO + DEX | 0.003 | 0.000 | 0.000 | 0.000 |
| CHL + DEX/TRO | NS | 0.017 | 0.004 | 0.000 |
| CHL + TRO/CHL + TRO + DEX | 0.045 | NS | NS | NS |
| CHL + TRO/TRO | NS | NS | NS | NS |
| CHL + TRO + DEX/TRO | 0.010 | 0.015 | NS | NS |

MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL: chlorpromazine; NS: not significant.

**TABLE 13**
***P* Values (Calculated Using the Wilcoxon Matched Pairs Test) of Individual Comparisons within Groups with Total Nausea and Emesis Control**

| | *P* values | | | | | |
|---|---|---|---|---|---|---|
| Treatment group | Emesis Day 1/Day 3 | Emesis Day 3/Day 7 | Emesis Day 7/Day 15 | Nausea Day 1/Day 3 | Nausea Day 3/Day 7 | Nausea Day 7/Day 15 |
| MET + DEX | 0.002 | 0.000 | NS | 0.000 | NS | NS |
| MET + TRO | 0.000 | NS | NS | 0.000 | NS | NS |
| MET + TRO + DEX | 0.000 | NS | NS | 0.000 | NS | NS |
| CHL + DEX | 0.000 | 0.000 | NS | 0.000 | NS | NS |
| CHL + TRO | 0.000 | NS | NS | 0.000 | NS | NS |
| CHL + TRO + DEX | 0.000 | NS | NS | 0.000 | NS | NS |

MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL: chlorpromazine; NS: not significant.

**TABLE 14**
**Adverse Effects during The Study**

| | MET + DEX | TRO | MET + TRO | MET + TRO + DEX | CHL + DEX | CHL + TRO | CHL + TRO + DEX |
|---|---|---|---|---|---|---|---|
| Dizziness | 1 | 1 | 2 | 1 | 1 | 1 | 1 |
| Constipation | 1 | 2 | 8 | 6 | 2 | 3 | 2 |
| Extrapyramidal symptoms | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Weakness | 12 | 7 | 8 | 2 | 17 | 7 | 6 |

MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL: chlorpromazine.

TRO groups, and one patient each from the MET+DEX+TRO,CHL+DEX, and CHL+TRO groups after the third treatment day.

### Tolerability

All antiemetic drugs were well tolerated. All observed side effects were mild, self-limited, and their severity did not force any patient to withdraw from the study. The occurrence of weakness was higher in the MET+DEX and CHL+DEX groups. Episodes of constipation also occurred more frequently in the TRO+MET, TRO+MET+DEX, and TRO groups (8, 6, and 7 patients, respectively) than in the other groups(Table 14). These differences did not reach statistical significance.

## DISCUSSION

The aim of this study was to compare the clinical efficacy of TRO with that of commonly used MET- and CHL-containing antiemetic cocktails in the prevention of emesis associated with far advanced cancer. The side effect profiles of the three antiemetic regimens also were compared.

The study design is compromised methodologically, primarily through lack of blinded experimentation, and by the fact that nausea has been measured incompletely (i.e., only the duration of nausea was evaluated and not the intensity). Nonetheless, there are appear to be several clinically useful guidelines supported.

The ''ideal'' agent for the treatment of nausea and emesis should be highly efficacious, devoid of disturbing side effects, and easy to administer. Cost should not be a barrier to use. In comparison with high dose MET- or CHL-based antiemetic regimens, the 5-HT3 receptor antagonists have some therapeutic advantage in every one of the important criteria mentioned earlier. In particular, they have a major side effect advantage over conventional antiemetics. Effective antiemetic control can be achieved without the sedation or extrapyramidal symptoms associated with prolonged administration of high dose CHL or MET. The simplicity and convenience of TRO administration provides particular benefits both to the patient and medical and nursing staff.

By the end of the fifteenth day, total emesis control was obtained in 24% of MET+DEX patients, in 65.8% of TRO patients, in 84% of TRO+MET patients, in 92% of TRO+MET+DEX patients, in 32.5% of CHL+DEX patients, in 82% of TRO+CHL patients, and in 92.5% of TRO+CHL+DEX patients (Fig. 1). Total control of nausea was achieved in 18% of MET+DEX patients, in 65.8% of TRO patients, in 74% of TRO+MET patients, in 87% of TRO+MET+DEX patients, in 17.5% of

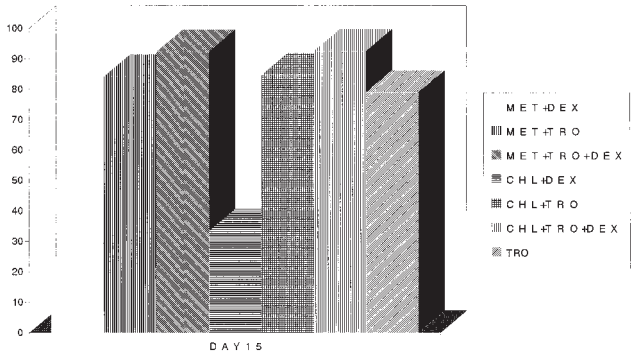


**FIGURE 1.** Total emesis control at the end of the study. MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL; chlorpromazine.

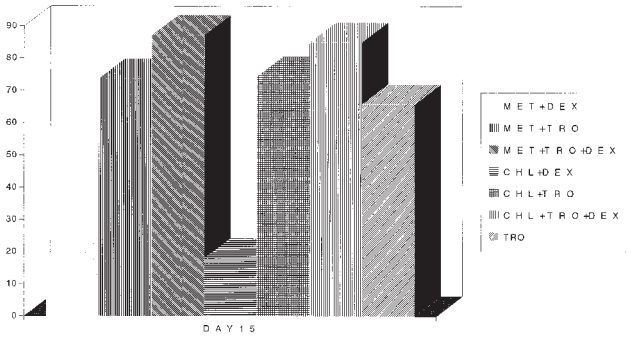


**FIGURE 2.** Total nausea control at the end of the study. MET: metoclopramide; DEX: dexamethasone; TRO: tropisetron; CHL; chlorpromazine.

CHL+DEX patients, in 72.5% of TRO+CHL patients, and in 85% of TRO+CHL+DEX patients (Fig. 2). Moreover, the combinations of TRO, TRO+MET, TRO+MET+DEX, TRO+CHL, and TRO+CHL+DEX succeeded in providing total control of nausea and emesis in the majority of the patients after the first day of the treatment day, which has great clinical significance. More specifically for the TRO, TRO+MET, TRO+MET+DEX, TRO+CHL, and TRO+CHL+DEX groups there were no significant differences between the third and the fifteenth day in total nausea and emesis control. For the MET+DEX and CHL+DEX groups there were no significant differences between the seventh and the fifteenth day in total nausea and emesis control.

This study raises important issues when attempting to decide which antiemetic therapy to choose for an individual patient. To understand these results it is useful to identify the possible underlying mechanisms.

The mechanism of nausea is not well understood. Nausea is mediated by the autonomic nervous system and is accompanied by flushing, perspiration, pallor, gastric stasis, and tachycardia. However, retching and vomiting are coordinated through the somatic nervous system.

Antiemetics may be divided by their main site of action into those that act on the chemoreceptor trigger zone (CTZ), which is situated in the medulla in the floor of the fourth ventricle, or the vomiting center (VC), which lies deeper in the medulla. However, there is considerable overlap.[13]

MET works by binding dopamine receptors in the CTZ, as well as by peripheral stimulation of gastrointestinal mobility.[14] It increases tone in the gastroesophageal sphincter, and thus reduces any tendency to reflex, increases gastric emptying, and causes dilatation of the proximal duodenum. At high doses MET is a far more effective antiemetic, and is believed to act by blocking both dopamine and 5-HT3 receptors. However, at high doses, the incidence of extrapyramidal syndromes increases.

Phenothiazines, such as CHL, also are effective antiemetic agents, but their widespread use has been limited by a number of side effects. Given at high doses orally or parenterally, they may cause hypotension as well as extrapyramidal symptoms, akathisia, and drowsiness.

5-HT3 receptor antagonists are very selective, and have a strong affinity for the 5-HT3 receptor. The 5-HT3 receptor antagonist TRO is considered to exert its action by interrupting the vomiting reflex in two ways: by blocking the emetogenic information transfer reaching the VC via the vagal nerve and by reducing the detection and integration of incoming information in the VC.[15]

As it has been stated before, in this study emesis was not due to metabolic or electrolytic disturbances, cranial causes, bowel obstruction, or drug intake. In this stage of the disease mechanical factors such as increase in tumor dimensions, external pressure, gastric distention, and stomach evacuation delay are responsible for the occurrence of emesis. The symptoms induced by gastric irritation have a peripheral etiology via nociceptors in the gastric wall and the vagus nerve, and also sympathetic afferents. In this case phenothiazines, anticholinergics, and antihistamines appear to provide the most clinical benefit. Evidence also exists for a direct role of 5-HT3 receptors in the area postrema in emesis.[16] 5-HT3 receptors also have been found on vagal afferent terminals[17] and it may be that 5-HT3 inhibits gastric emptying. It also is known that in this stage of the disease, the circulation of putative ''toxins'' stimulate the chemoreceptor trigger zone and therefore the VC. Inhibition of 5-HT3 receptors peripherally and centrally located, by TRO with or without DEX, in combination 1) with the muscarinic cholinergic action of CHL or 2) with the inhibition of dopamine receptors in CTZ and stimulation of the gastric

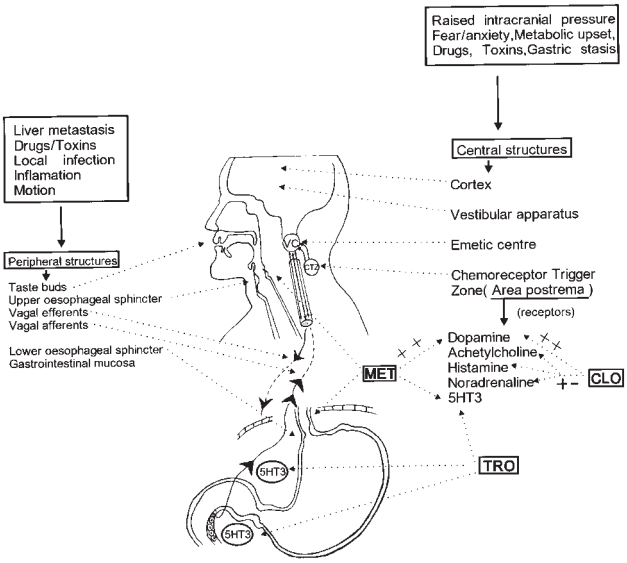


**FIGURE 3.** Model of the emetic process, action mechanisms, and action sites of the most frequently used antiemetic drugs. TRO: tropisetron; MET: metoclopramide; CLO: chlorpromazine.

mobility by MET, is why these combinations appear to have such good results in controlling these symptoms. Figure 3 shows the mechanisms of antiemetic action and action sites for each medication used in the current study.

If emesis is persistent then a combination of antiemetics with different sites of action may be more effective than a single agent. Furthermore, although the mechanism of action is unknown, DEX is a useful tool in the treatment of intractable nausea and emesis in patients with advanced cancer.

In the future, the methodology and therapeutic resources developed for the treatment of chemotherapy-induced emesis should focus on chronic nausea and emesis. Further studies should focus on characterizing this syndrome more clearly. It is likely that the presence of cachexia, chronic pain, and cognitive failure all have major influences on the assessment and management of nausea and emesis.

Continued research incorporating pharmacoeconomic and quality of life endpoints using serotonin antagonists in combination with other antiemetic agents will help to define their optimal cost-effective role in the palliative setting.

As is the case with the majority of existing antiemetics, only continued preclinical and clinical research will allow the best use of the unique characteristics of TRO. However, existing data already indicate that the compound represents the treatment of choice in persistent nausea and emesis in patients with terminal cancer and in combination with DEX has achieved better therapeutic results than standard antiemetic first-line treatment. These important observations form a solid basis for further therapeutic progress.

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