A randomized, double-blind trial assessing the efficacy and safety of sublingual metopimazine and ondansetron in the prophylaxis of chemotherapy-induced delayed emesis

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The prevention of delayed emesis following chemotherapy remains an important challenge. This randomized, double-blind, double-dummy, multicenter study was designed to compare the efficacy and tolerance of metopimazine and ondansetron at preventing nausea and emesis in patients receiving chemotherapy. Two hundred patients were evaluated for efficacy: 103 patients received metopimazine (7.5 mg × 2 t.i.d.) and 97 received ondansetron (8 mg b.i.d.) for 5 days. Patients were asked to report episodes of nausea and emesis in a diary, and quality of life (QoL) was evaluated using the Functional Living Index – Emesis questionnaire. The incidence of complete response (defined as no nausea and emesis for 5 days) did not differ between the two treatment arms (53.4% for metopimazine versus 49.5% for ondansetron; $P=0.58$). No significant difference was found for the incidence of emesis (23.3% for metopimazine versus 30.9% for ondansetron) or QoL. Tolerance was as expected for both drugs and comparable, except for the incidence of gastrointestinal disorders, which was significantly lower in the metopimazine group (19.4 versus 32.7%; $P=0.03$). We conclude that metopimazine is an alternative to ondansetron that is better tolerated for the prevention of delayed emesis in patients receiving chemotherapy.
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Introduction

Nausea and emesis are among the most inconvenient adverse effects (AEs) experienced by cancer patients treated with cytotoxic drugs [1,2]. Acute emesis can occur in the first 24 h following chemotherapy and delayed emesis can begin or persist for more than 24 h after chemotherapy. While the majority of patients suffering from acute emesis are adequately managed [3,4], only 45% of patients do not experience any delayed nausea or emesis vomiting with currently available anti-emetic treatments [2,5,6].

Risk factors for delayed emesis include female gender, young age, poor control of emesis during prior chemotherapy administration and type of cytotoxic agents used [2,7,8]. Chemotherapeutic drugs have been classified according to their emetic potential [5,9]. Delayed emesis is primarily associated with cisplatin, cyclophosphamide, anthracyclines and certain other drugs such as ifosfamide. Although the risk of delayed emesis is dose related, it is observed with standard doses of high-risk drugs.

International guidelines recommend anti-emetic pharmacotherapy for prevention and treatment of chemotherapy-induced delayed emesis [5,6,10]. The treatment of delayed emesis is based on the emetic potential of the cytotoxic agent administered. The American Society of Clinical Oncology recommends the administration of corticosteroid monotherapy, metoclopramide or serotonin (5-HT) receptor antagonists. The combination of a corticosteroid plus either metoclopramide or a 5-HT_3 antagonist is, however, recommended for the prevention of delayed emesis associated with cisplatin administration [5]. More recently, NK1 tachykinin receptor antagonists have been introduced for the control of chemotherapy-induced emesis [11].

Delayed emesis has been associated with significant distress in cancer patients, leading to quality of life (QoL) detriments and reduced treatment compliance [2]. At present, there are few treatment options with proven efficacy and additional research into the prevention of emesis is strongly encouraged [5,12–14].

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Metopimazine is also indicated for the prevention of acute chemotherapy-induced emesis and is available in certain countries. Like metoclopramide, this drug is a selective dopamine receptor antagonist at therapeutic doses, but differs from metoclopramide in that it does not cross the blood–brain barrier (BBB) (Joliet *et al.*, submitted) and thus does not show centrally mediated side-effects. The sublingual formulation of metopimazine may be particularly suitable for the treatment of delayed emesis. This pharmaceutical form is rapidly absorbed and transformed into metopimazinic acid (which does not penetrate the central nervous system) within 30 min of administration. The biotransformation rate after sublingual administration is 88.9%. The acid metabolite shows a linear relationship with metopimazine dose and an elimination half-life of around 4.5 h. The activity of metopimazine in chemotherapy-induced delayed emesis has been assessed in combination with other anti-emetic drugs in several clinical trials [14–20]. Findings from these studies indicate that the addition of metopimazine to the anti-emetic regimen elicits better control of delayed nausea and vomiting.

Previous studies have not specifically addressed delayed emesis, since patients were randomized to treatment prior to the chemotherapy rather than between the acute and delayed phase. Since acute emesis is an identified risk factor for delayed emesis, a treatment effect on delayed emesis may have been secondary to a primary effect on acute emesis. For this reason, it is important to determine the specific effect of metopimazine on delayed emesis. A recent observational study [21] has demonstrated that sublingual metopimazine is at least as effective as ondansetron in the specific control of delayed emesis when used in combination with corticosteroids. We therefore wished to complement this study using a parallel-group design in order to compare directly the use of the two treatments without concomitant corticosteroid use. The aim of this study was to compare the efficacy and safety of sublingual metopimazine tablets to sublingual ondansetron as monotherapy in patients receiving chemotherapy.

Patients and methods

Patients

Adult cancer patients receiving moderately to highly emetic chemotherapy were considered for inclusion in this trial (levels 3–5 of the Hesketh classification [9] or a combination of level 2 cytotoxic agents). Patients had to have a good performance status (WHO performance status 0–2). Patients were not included if they had obstructive bowel disease, brain or meningeal metastasis, nausea and vomiting in the 24 h before chemotherapy, concurrent long-term therapy with corticosteroids (unless given before a taxane infusion), neuroleptics, or pain requiring a non-stable dose of opioid therapy.

All patients provided written, informed consent before study entry. The protocol was reviewed and approved by a National Ethics Committee.

Treatment of acute emesis

Treatment for preventing acute emesis was not standardized, but left to each investigator's discretion; however, treatment was expected to conform to recognized international guidelines [5,6,10].

Delayed anti-emetic therapy

Patients were randomly assigned to receive one of the following anti-emetic therapies during a 5-day treatment period for the prophylaxis of delayed emesis (i.e. that starting 24 h after chemotherapy on days 2–6): oral metopimazine, two sublingual 7.5-mg tablets every 8 h, giving a total dose of 45 mg/day, or ondansetron, one sublingual 8-mg tablet every 12 h, giving a total dose of 16 mg/day. A double-dummy design was used to ensure satisfactory blinding in the study, with each patient receiving four tablets per day at a fixed time, corresponding to the active drug for the study arm and a placebo of the comparator.

Data collection

At an inclusion visit, data on demographic parameters, disease and treatment antecedents were identified from patient records. Additional information on risk factors and antecedents of vomiting was collected by the investigator during an interview with the patient using a standard structured questionnaire.

All patients were asked to report in a daily diary on the occurrence of nausea and vomiting episodes during a period of 5 days. Vomiting was measured by counting the number of vomits (excluding dry retches) in each 24-h period. Nausea was defined as a feeling of sickness accompanied by a premonitory sensation of gastric reflux. Use of rescue medication was not considered in the outcome. They were also required to complete, at the end of the treatment, the Functional Living Index – Emesis (FLIE) questionnaire; this self-assessment questionnaire includes 18 items evaluating the impact of nausea and emesis on a patient's QoL. Additionally, patients were asked to evaluate their health status daily on a visual analog scale from 0 to 10 (0 = worst health status and 10 = best health status).

The primary endpoint was the efficacy parameter, assessed as treatment success or failure. Success was defined as the effective prophylaxis of nausea and vomiting during the 5 days following chemotherapy (i.e. no nausea and no vomiting). AEs were assessed by investigators at each study site based on their clinical judgment and patient-derived information, and then validated centrally by the coordinating investigator.

Treatment compliance was evaluated by counting the capsules and tablets returned by the patients at the final visit.

Statistical analysis

The likely rate of success was estimated to be 60% in the most active group and, therefore, using the formula of Casagrande and Pike [22] with 80% power using a 5% level of significance, the number of evaluable patients necessary was determined to be 100 patients per treatment group. A sample size of 220 enrolled patients, taking into account the potential for drop-out patients, was therefore estimated in order to detect a difference of 20% between the two treatment arms.

Three study populations were considered in the study. The randomized population consisted of all patients randomized. The safety population was defined as all randomized patients who had received at least one dose of study medication. The intent-to-treat (ITT) population was defined as all randomized patients who had received at least one dose of study medication and had provided at least one post-randomization efficacy outcome measure. The primary analysis was performed on the ITT population. Patients were stratified according to previous chemotherapy administration.

Quantitative and semiquantitative parameters were analyzed using Student's *t*-test or a non-parametric Mann–Whitney test. Qualitative variables were assessed using a χ^2-test with a Yates correction where necessary.

Results

Patient characteristics

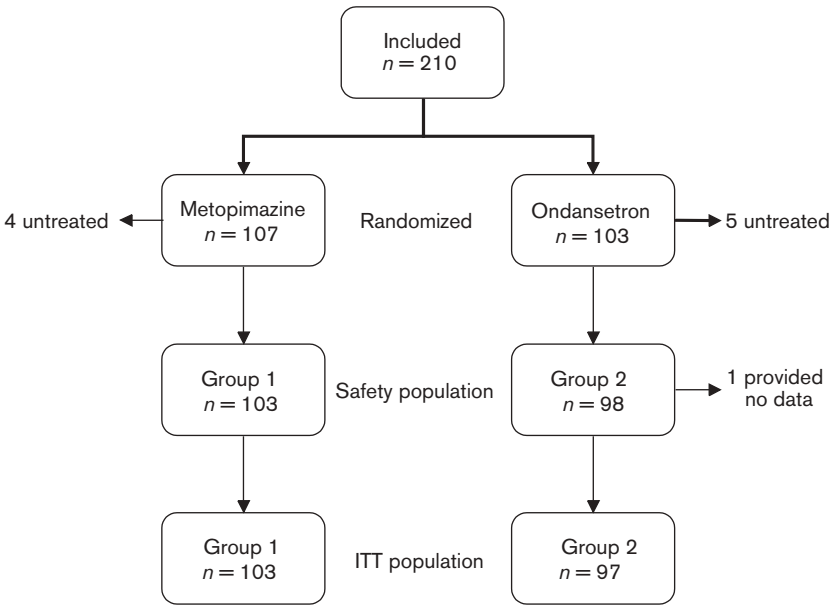
Between June 2003 and November 2003, 210 cancer patients from 14 centers in France were enrolled into the study. The flow of patients through the study is presented in a patient flow diagram in Fig. 1. One-hundred and seven patients were randomized to metopimazine and 103 to ondansetron. These constitute the randomized population.

Four patients in the metopimazine group and five patients in the ondansetron group failed to initiate treatment. The remaining 201 patients constitute the safety population. Furthermore, no efficacy data were collected for one patient who discontinued treatment. Overall, 200 patients (103 in the metopimazine group and 97 in the ondansetron group) were thus included in the ITT population. No major protocol deviations were observed during the study.

Demographic and clinical features of the ITT population are summarized in Table 1. No between-group differences were observed for any of these variables. Patients with a wide variety of malignancies were included, the most common being breast cancer (48%) and colon tumors (18%). In addition, 35% of patients had metastatic disease; liver metastasis was found in 55% of these patients (Table 1).

Some patients were identified to have characteristics known to be associated with a poor prognosis for emesis

Fig. 1



Patient flow diagram.

control, including emotional problems (18%) and motion sickness (7%). Alcoholism, which is associated with protection against drug-induced emesis, was infrequently encountered in the study population (3%). Among the 144 women, 85% had been pregnant at least once, of whom 24% had experienced emesis during pregnancy. The incidence of all these prognosis factors tended to be slightly higher in the metopimazine group (Table 1).

Chemotherapy history for the ITT population is presented in Table 2. Almost half of the patients (42%) were receiving chemotherapy for the first time; the remaining 117 patients had been previously treated with chemotherapy (88 with the current chemotherapy regimen). Among the latter patients, 69 (78%) patients had previously received an anti-emetic treatment, including a setron alone or in combination with a steroid and/or a prokinetic drug and/or metoclopramide or metopimazine. In previous chemotherapy cycles, 32% of patients had no nausea during or after chemotherapy, 22% acute nausea, 35% delayed nausea, and 11% acute and delayed nausea. Regarding emesis, 72% had no emesis, 14% acute emesis, 10% delayed emesis, and 5% acute and delayed emesis. There was no difference between treatment groups in the incidence of emesis or nausea.

Data on current chemotherapy regimens in the randomized population are presented in Table 3. Overall, 86% of the patients were treated with chemotherapy with a high emetogenic potential (i.e. level 4 and 5 of the Hesketh classification). There were no significant statistical differences in the emetic potential of the chemotherapy. The vast majority of patients were receiving combinations of more than one cytotoxic drug; 11 patients randomized to metopimazine and 14 patients randomized to ondansetron received a single drug. The most frequently used chemotherapy treatment regimens are listed in Table 3. The single most widely used drugs were 5-fluorouracil (5-FU), cyclophosphamide and doxorubicin. There were no obvious differences in chemotherapy regimens between the two groups.

Data on acute anti-emetic treatment for the randomized population are presented in Table 4. In all, 198 patients (94%) received an anti-emetic treatment. In all but three of these patients this was a setron, principally ondansetron, given alone (25%) or in combination with a corticosteroid (36%). Corticosteroids were taken by 136 patients (65%) and 37 received clorazepate as well (18%). Prokinetic agents (alizapride, metoclopramide) were used more rarely (17% of patients). One patient received metopimazine as an anti-emetic treatment. There was no statistically significant difference in the use of anti-emetic treatment between the two treatment groups ($P = 0.3$).

Treatment compliance was high at 91.7%, and was not significantly different between the two treatment groups. Seventy-one patients (40 in the metopimazine group and 31 in the ondansetron group) had a compliance lower than 100% for the following reasons: 25 because no nausea after some days of treatment, 18 due to AEs, 17

Table 1 Patient characteristics at baseline in the ITT population

	Metopimazine ($n=103$)	Ondansetron ($n=97$)
Demographics		
age (years) (mean ± SD)	58.9 ± 11.9	57.8 ± 11.9
female/male [*n* (%)]	72 (72.9)/31 (30.1)	65 (67.0)/32 (33.0)
weight (kg) (mean ± SD)	65.7 ± 13.8	68.7 ± 13.8
height (m) (mean ± SD)	164 ± 7	165 ± 8
BMI (mean ± SD)	24.4 ± 4.4	25.2 ± 4.7
Localization of the primary tumor [*n* (%)]		
breast	49 (47.6)	46 (48.5)
lung	5 (4.9)	6 (5.8)
colorectal	23[a] (22.4)	13 (14.6)
other	17[a] (26.2)	32 (31.1)
Cancer stage [*n* (%)]		
metastatic disease	36 (37.1)	31 (35.1)
Risk factors [*n* (%)]		
affective disorders	21 (20.4)	15 (18.0)
motion sickness	8 (7.8)	5 (6.6)
emesis during pregnancy	16 (29.6%; $n=54$)[b]	11 (22.4%; $n=49$)[b]
alcohol consumption (glasses/day) (mean ± SD)	0.2 ± 0.5	0.3 ± 0.8

The difference between the two treatment groups was not significant with respect to all parameters.
[a]One patient in the metopimazine group was reported as having two primary tumors ('colorectal' and 'other').
[b]*n* values refer to number of patients who had been pregnant.

Table 2 Previous chemotherapy history for the ITT population

	Metopimazine ($n=103$)	Ondansetron ($n=97$)
Previous chemotherapy exposure [*n* (%)]	$n=103$	$n=97$
chemotherapy naive	43 (41.7)	40 (41.2)
any previous chemotherapy exposure	60 (58.3)	57 (58.8)
Previous current chemotherapy exposure	48 (46.6)	40 (41.2)
Period between the first chemotherapy and inclusion (months) [*n* (%)]	$n=60$	$n=57$
<2	19 (31.7)	21 (36.8)
2–5	17 (28.3)	9 (15.8)
>5	24 (40.0)	27 (47.4)
No. cycles of current chemotherapy [*n* (%)]	$n=48$	$n=40$
1	15 (31.3)	9 (22.5)
2 or 3	16 (33.3)	17 (42.5)
>4	17 (35.4)	14 (35.0)
Previous anti-emetic treatment with current chemotherapy [*n* (%)]	40 (83.3) ($n=48$)	29 (72.5) ($n=40$)
Tolerance during previous cycles of current chemotherapy [*n* (%)]	$n=48$	$n=40$
nausea		
none	14 (29.2)	14 (35.02)
acute only	10 (20.8)	9 (22.5)
delayed only	19 (39.6)	12 (30.0)
acute and delayed	5 (10.4)	5 (12.5)
emesis		
none	36 (75.0)	27 (67.5)
acute only	6 (12.5)	6 (15.0)
delayed only	5 (10.4)	4 (10.0)
acute and delayed	1 (2.1)	3 (7.5)

Percentages are calculated with respect to the sample sizes indicated in the subheadings. No significant differences between the two treatment groups were noted for any parameter.

Table 3 Chemotherapy in the randomized population [*n* (%)]

	Metopimazine ($n=107$)	Ondansetron ($n=103$)	Total ($n=210$)
5-Fluorouracil	64 (59.8)	66 (64.1)	130 (61.9)
+ cyclophosphamide + epirubicin	11 (10.2)	13 (12.7)	24 (11.5)
+ irinotecan	9 (8.4)	10 (9.7)	19 (9.0)
+ cyclophosphamide + epiadriamycin	8 (7.5)	9 (8.7)	17 (8.1)
+ oxaliplatin	8 (7.5)	3 (2.9)	11 (5.3)
Cyclophosphamide	51 (47.7)	52 (50.5)	103 (49.0)
+ doxorubicin	18 (16.8)	17 (16.5)	35 (16.7)
+ 5-FU + epirubicin	11 (10.2)	13 (12.7)	24 (11.5)
+ 5-FU + epiadriamycin	8 (7.5)	9 (8.7)	17 (8.1)
+ adriamycin	7 (6.5)	3 (2.9)	11 (5.3)
Doxorubicin	22 (20.6)	20 (19.4)	42 (20.0)
+ cyclophosphamide	18 (16.8)	17 (16.5)	35 (16.7)
Epirubicin	13 (12.2)	15 (14.6)	28 (13.3)
+ 5-FU + cyclophosphamide	11 (10.2)	113 (12.7)	24 (11.5)
Irinotecan	17 (15.9)	11 (10.7)	27 (12.9)
+ 5-FU	9 (8.4)	10 (9.7)	19 (9.0)
Epiadriamycin	10 (9.4)	11 (10.7)	21 (10.0)
+ 5-FU + epiadriamycin	8 (7.5)	19 (8.7)	17 (8.1)
Oxaliplatin	15 (14.0)	6 (5.8)	21 (10.0)
+ 5-FU	8 (7.5)	3 (2.9)	11 (5.3)
Carboplatin	5 (4.7)	7 (6.8)	12 (5.7)
Adriamycin	7 (6.5)	4 (3.9)	11 (5.2)
+ cyclophosphamide	7 (6.5)	3 (2.9)	10 (4.8)
Docetaxel	4 (3.74)	7 (6.8)	11 (5.2)
Cisplatin	2 (1.9)	8 (7.8)	10 (4.8)
Gemcitabine	3 (2.8)	6 (5.8)	9 (4.3)
Single cytotoxic agent	11 (10.3)	14 (13.6)	25 (11.9)
Hesketh level of emesis-inducing chemotherapy			
2	2 (1.9)	4 (3.9)	6 (2.9)
3	10 (9.3)	13 (12.6)	23 (11.0)
4	54 (50.5)	38 (36.9)	92 (43.8)
5	41 (38.3)	48 (46.6)	89 (42.4)

Only the most frequent chemotherapy regimens (more than five treatments in either group) are listed. Apart from those listed under 'single cytotoxic agent', all patients received associations of treatments. Data on chemotherapy are non-exclusive and all patients are listed for each drug entry.

Table 4 Acute emesis treatment in the randomized population [*n* (%)]

	Metopimazine ($n=107$)	Ondansetron ($n=103$)
Any acute emesis treatment	102 (95.3)	96 (93.2)
Ondansetron (alone or in combination)	82 (76.6)	70 (68.08)
+ methylprednisolone	23 (23.6)	21 (21.8)
+ prednisolone	–	1 (1.0)
Granisetron (alone or in combination)	19 (17.8)	24 (23.3)
+ methylprednisolone	13 (12.8)	17 (17.6)
+ prednisolone	–	1 (1.0)
Methylprednisolone (alone or in combination)	69 (64.5)	67 (65.1)
Clorazepate (+ ondansetron + methylprednisolone)	21 (20.6)	16 (16.7)
Alizapride (various combinations)	11 (10.3)	12 (11.7)
Metoclopramide (alone or in combination)	5 (4.7)	8 (7.8)
Metopimazine	–	1 (1.0)

Since patients could receive combinations of anti-emetic drugs, these classes are not exclusive. The difference between the two treatment groups was not significant.

due to insufficient clinical response, eight due to the bad taste of tablets and three patients withdrew consent. No significant difference was observed between the two treatment groups ($P = 0.6$).

Efficacy

Control of delayed nausea and emesis

Complete control of emesis for 5 days was achieved in 53.4% of patients treated with metopimazine and 49.5% of patients treated with ondansetron. The difference between treatments was not statistically significant {3.9% [95% confidence interval (CI) −9.9; 17.8%]; $P = 0.58$; χ^2-test}. When assessing the rate of success for nausea and emesis separately, no statistically significant difference was observed [nausea: 2.6% (95% CI −11.1; 16.3%; $P = 0.7$; χ^2-test); vomiting: 7.6% (95% CI −4.7; 19.9%; $P = 0.2$; χ^2-test)]. The results are presented in Fig. 2.

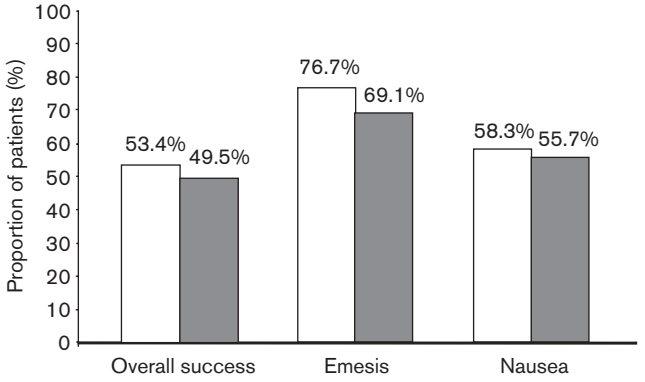
QoL and global evaluation of health status

There was no significant difference in QoL scores between the two treatment arms with respect to all 18 questionnaire items completed by the patients. The mean global score was 33.4 in the metopimazine group and 40.1 in the ondansetron group ($P = 0.33$). Similarly, the daily comparison of the global health status, as assessed by the patients, did not differ between the two treatment groups.

Safety

The proportion of patients in the safety population experiencing at least one AE was similar in both groups: 45.6% of patients in the metopimazine group and 42.9% in the ondansetron group ($P = 0.7$; χ^2-test). The most frequent AEs are listed Table 5.

Fig. 2



Percentage of overall success (no nausea and no vomiting), protection against nausea and protection against vomiting over the 5-day observation period. Open columns: metopimazine; filled columns: ondansetron. There were no significant differences between the metopimazine and ondansetron groups on any of the three outcome measures.

Table 5 Treatment-emergent AEs in the safety population [*n* (%)]

	Metopimazine ($n=103$)	Ondansetron ($n=98$)
Gastrointestinal disorders[a]	20 (19.4)[a]	32 (32.7)[a]
constipation	9 (8.7)	14 (14.2)
abdominal pain	3 (2.9)	12 (12.2)
diarrhea	3 (2.9)	5 (5.1)
Headache	6 (5.8)	8 (8.2)
Alopecia	15 (14.6)	13 (13.3)
Asthenia	3 (2.9)	6 (6.1)
Mucositis	5 (4.9)	9 (9.2)

Data are presented as number of patients. Only those AEs reported in more than five patients in either study group are listed.
[a]$P=0.03$ (χ^2-test).

The incidence of gastrointestinal disorders was significantly lower in the metopimazine group (19.4 versus 32.7%; $P = 0.03$; χ^2-test), particularly abdominal pain and constipation. No significant differences were observed between the two treatments groups with respect to headache, which was the other most common AE experienced by patients during this study.

Six serious (SAEs) occurred during the treatment (five in the ondansetron group and one in the metopimazine group) and three occurred after the end of the study. One SAE in the ondansetron group (laryngeal edema) was considered by the investigator to be probably related to the study treatment.

Overall, 18 patients discontinued their treatment due to AEs (eight patients in the metopimazine group and 10 in the ondansetron group). The main reasons for discontinuation were gastrointestinal disorders, headaches and pain (Table 6).

Table 6 Patients withdrawn for AEs

AE	Metopimazine ($n=8$)	Ondansetron ($n=10$)
Vomiting	3	–
Nausea and vomiting	–	2
Nausea	1	–
Headaches	1	1
Headaches and gastralgia	–	1
Intestinal obstruction	1	–
Flush	1	–
Palpitations/chills/headaches	1	–
Abscess of the left buttock	–	1
Abdominal and pelvic pain	–	1
Epigastralgia	–	1
Constipation	–	1
Laterothoracic pain	–	1
Laryngeal edema[a]	–	1

[a]Reported by the patient; not observed by the investigator.

Discussion

The aim of this study was to compare the efficacy and safety of metopimazine and ondansetron for the prevention of delayed emesis in patients receiving chemotherapy. We found no difference between these two drugs (53.4% for metopimazine and 49.5% for ondansetron; $P = 0.58$). This was not an equivalence trial; however, the lack of significant difference (95% CI –9.9; 17.8%) means that the probability of the real difference between the two drugs exceeding 9.9% in favor of ondansetron or 17.8% in favor of metopimazine was less than 5%.

Complete control of emesis was slightly lower in both treatment groups than that reported in the literature [2]. This may be explained by (i) use of chemotherapeutic regimens that were on average highly emetogenic and (ii) the fact that no corticosteroids were allowed during the treatment of delayed emesis, since the aim of the study was to perform the most direct comparison between metopimazine and ondansetron. Indeed, another study compared the activity of metopimazine and ondansetron in controlling delayed emesis when used in association with corticosteroids [21]. This study showed that 74% of patients had a complete control of emesis with the combination of metopimazine plus methylprednisolone compared to 58% of patients who were controlled with the combination of ondansetron plus methylprednisolone ($P = 0.02$). In another study comparing granisetron and metoclopramide in combination with corticosteroids [23], 73% of the patients taking granisetron plus corticosteroid and 75% of patients taking metoclopramide plus corticosteroid had complete control of emesis. It should be noted that recent consensus guidelines [24] recommend the use of corticosteroids in combination with a setron or NK1 receptor antagonist for the control of delayed emesis when highly emetogenic chemotherapeutic treatment regimens are used. The fact that corticosteroid combination was not used in this study thus limits the relevance of the results to optimal standards of care using associations.

As expected, tolerance of both drugs was good. As a consequence, treatment compliance was also good for all of the patients. Of note, metopimazine exhibited less gastrointestinal toxicity. This is a potential advantage of metopimazine over other drugs that have been tested as alternatives to setron in this setting, especially neuroleptics like metoclopramide, and it is due to the absence of any extrapyramidal effect with metopimazine.

Two recent studies have confirmed the pharmacological characteristics of metopimazine and explained the good safety profile of this product. The first study [25] showed that metopimazine is rapidly and almost totally biotransformed into the metabolite metopimazinic acid. In a second study, the penetration of metopimazine across the BBB was compared to other anti-emetic agents (Joliet *et al.*, submitted). The endothelial permeability coefficient for metopimazinic acid was very low (0.49), whereas values for domperidone and chlorpromazine were 44.9 and 47.7, respectively. For metoclopramide, very good penetration across the BBB was observed; the endothelial monolayer did not act as a barrier. These results confirm the lack of neuroleptic activity of metopimazine and explain the absence of central nervous system side-effects.

In this trial, we focused on delayed emesis and the study was not designed to evaluate protection against acute emesis, since the efficacy of metopimazine is clearly established in this indication [13–20]. For this reason, no data on acute emesis was collected and investigators were free to use whatever treatments they felt appropriate for the control of acute emesis. To simplify evaluation, we defined a treatment as successful if the patient reported no nausea and no emesis for 5 days. This is in accordance with international guidelines for anti-emetic therapy evaluation. Since acute emesis control is an important determinant of delayed emesis control, however, the absence of information on acute emesis and on whether the study treatments differed in their ability to control this represents a limitation of the study.

Another limitation of the study is the inclusion of a heterogeneous group of patients (naive or previously exposed, type of chemotherapy used, treatments for acute emesis). This reflects the variety in the type of patient treated routinely in the study centers and was a necessary constraint to facilitate inclusion. Notably, previous chemotherapy experience, antecedents of emesis, control of acute emesis and use of corticosteroids in the acute phase could influence delayed emesis outcome. Although these factors were not standardized by the study protocol, they were balanced between the two treatment groups and are unlikely to have influenced the outcome of the study. The heterogeneity of the study sample is an advantage in considering how the results obtained could be related to routine care.

Further studies using more highly selected groups of patients may help to identify which groups, if any, are the most responsive to different anti-emetic treatments. In particular, it would be interesting to evaluate metopimazine in patients using less intensely emetogenic chemotherapy regimens, where efficacy may be expected to be higher. Indeed, the unexpectedly high proportion of patients using highly emetogenic chemotherapy included in the present study (86%) precludes drawing conclusions on the efficacy of the study treatments with respect to moderately emetogenic chemotherapy. Future studies would also be useful to compare the effectiveness of metopimazine to that of NK1 tachykinin receptor antagonists.

The total dosage of metopimazine delivered during the study was 45 mg/day. This is a relatively low dose compared to many previous studies in chemotherapy-related emesis, which have used doses of metopimazine as high as 120 mg/day [14–16,19]. Other studies performed in cancer patients with metopimazine however, that assessed dosages of 15, 30 and 45 mg/day of metopimazine versus placebo have also demonstrated efficacy [26–28], and the dose of 45 mg/day corresponds to the approved anti-emetic dose in France. Although the dose of 45 mg was active and well tolerated, it cannot be excluded that higher doses of metopimazine could possibly lead to higher response rates.

In conclusion, the routine prescription and selection of anti-emetic agents should ideally be based upon efficacy, tolerance, cost and convenience. This study shows that metopimazine is an alternative to ondansetron for the treatment of chemotherapy-induced delayed nausea and vomiting, with similar efficacy and better tolerability.

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